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The Journal of Allergy

VOL. 11 MARCH, 1940 No. 3

Original Articles

SEROLOGIC CHANGES IN HAY FEVER CASES TREATED OVER A PERIOD OF YEARS

WILLIAM B. SHERMAN, M.D., ARTHUR STULL, PH.D., AND ROBERT A. COOKE, M.D.
NEW YORK, N. Y.

THE serologic changes resulting from the treatment of hay fever with injections of pollen extracts have been described by Cooke, Barnard, Hebald, and Stull[1] in a previous publication from this clinic. In their cases, the amount of skin-sensitizing antibody as measured by the dilution test was practically unchanged by the injections. However, the amount of pollen extract required to neutralize the skin-sensitizing antibody of the serum was definitely greater after treatment. This change was attributed to the development during treatment of a blocking antibody which inhibited the reaction between the antigen and the sensitizing antibody.

These observations have been confirmed by Harley[2] and by Langner and Kern.[3] The rise in the neutralization value of the serum during treatment has also been reported by Schmidt and Lippard[4] who considered the neutralization a measure of the amount of skin-sensitizing antibody.

Furthermore, Cooke, Loveless, and Stull[5] showed that injections of pollen extract into normal nonallergic human subjects produced a blocking antibody without the presence of any skin-sensitizing antibody. Cohen[6] produced a similar antibody by injecting pollen extract into sheep. Lichtenstein[7] attempted unsuccessfully to produce such a serologic change by intravenous injections of pollen extract into nonallergic men. This negative result may have been due to differences in dosage and technique.

Although confirming the existence of a blocking antibody in the serum of some hay fever patients after treatment, Harley[2, 8] has maintained that in the majority of cases the amount of skin-sensitizing antibody in the serum was reduced by treatment, and has considered this the most important change. Markin[9] also reported a decrease of the skin-sensitizing antibody after treatment. On the other hand,

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Presented before the meeting of the Society for the Study of Asthma and Allied Conditions, April 29, 1939, Atlantic City, N. J.

Levine and Coca[10] and Gay and Chant[11] found the skin-sensitizing capacity of the serum unchanged or increased after pollen injections.

The workers cited have compared serum taken before treatment with that obtained after a course of injections over a period of three months to one year. The present investigation is an extension of the work of Cooke, Barnard, Hebald, and Stull[1] to include sera of hay fever patients treated over longer periods of time. Intracutaneous tests with pollen extract, titration of skin-sensitizing antibody by the dilution of sera, and the quantitative neutralization of skin-sensitizing antibody with pollen extract were carried out by essentially the same technique.

SELECTION OF CASES

Two groups of cases were studied. The larger group (Group 1) consisted of fifty-five patients selected because of outstandingly good clinical results during treatment. These patients had been treated for from two to twenty-three years and had shown progressive improvement from year to year, leading in many cases to a complete absence of symptoms. Consequently their sera were expected to show the maximum effects of treatment by pollen injection. However, in only a few of the more recent cases had a serum for comparison been taken before treatment was started.

Group 2, including some of the same cases, consisted of eight patients treated for from two to five years with satisfactory clinical results, whose sera had been obtained for study before treatment was started and at intervals during treatment. This group served to bridge the gap between those treated only one year and the longer treated cases of Group 1.

All of the patients gave histories of typical hay fever during the pollinating seasons of ragweed or of the grasses or both and, before treatment, had shown marked reactions to intracutaneous tests with the corresponding pollen extract. Those sensitive to ragweed pollen were treated with a mixture of equal parts of extracts of giant and low ragweed pollens; those sensitive to grass pollen, with an extract of timothy pollen. In some cases the injections of pollen extract were given weekly for three or four months before and during the pollen season of each year (seasonal treatment); in others, the injections were given at longer intervals throughout the year (perennial treatment). In most cases the maximum dose of pollen extract was 10,000 to 20,000 protein units,* but a few cases were kept at lower doses because they had had constitutional or marked local reactions to the injections. Some of the cases were also treated with other antigens to which they were sensitive, but in every case selected, the outstanding sensitivity was to the pollens. The essential facts of the clinical histories are tabulated in Table I.

*1 protein unit=0.00001 mg. of protein nitrogen.[12]

The cases selected for Group 1 had had little or no hay fever during the last two or three seasons under treatment. All of them resided during the hay fever season in the vicinity of New York or in localities where there was an abundance of pollen, and they did not depend upon air filters or other mechanical devices to avoid contact with pollen. Therefore, their improvement was assumed to be due to the injection treatment. In judging the results in the ragweed cases, particular stress was laid on the years 1936 and 1938, as, during those years, pollen counts in New York City showed unusually high concentrations of ragweed pollen in the atmosphere.

Three patients were definitely sensitive to and were treated with both grass and ragweed pollens. In tabulating the results, each of the sensitivities has been considered separately as a case.

Because of the long period covered by the treatment of the patients of Group 1, it was not possible to follow a comparable control group without treatment. As a basis of comparison, sera of thirty-one untreated cases of hay fever were studied. These cases gave clinical histories and reactions to intracutaneous pollen tests comparable to those given by cases of Group 1 before treatment. The ages of these patients varied from 20 to 59 years and the duration of hay fever from one to twenty years. The data are given in Table IA.

GROUP 1

Changes in Skin Tests.—Skin tests, by the intracutaneous injection of approximately 0.01 c.c. of suitable dilutions of pollen extract, were done on all cases before and after treatment. The results, judged on the basis of size and shape of the wheals, are recorded in the clinical histories as slight, moderate, or marked.[13] It was often noted that the skin reactions in long treated cases were slow to develop and accompanied by less intense itching and erythema than in untreated cases. These differences were difficult to judge quantitatively and are not expressed in the readings of the tests.

The extracts used for testing prior to 1932 were standardized on the basis of total nitrogen content;[14] since 1932, they have been standardized by the protein nitrogen content. As the pollen extracts have been made in recent years, 0.02 to 0.03 mg. of total nitrogen corresponds approximately to 0.01 mg. or 1,000 units of protein nitrogen.[12] During the twenty-three years in which the tests were done, various modifications have been made in the methods of preparing extracts, so that the ratio of protein to total nitrogen may not have been the same. Any variations in the older extracts were probably such as would make them relatively less active than indicated by the analyses. This would have tended to lessen any decrease in the reactions to skin tests during treatment.

Because of these difficulties in quantitative comparison of the skin tests before and after treatment, the cases were merely divided into

TABLE I

SUMMARY OF CLINICAL DATA

CASE	SEX	BORN	HAY FEVER		INITIAL SKIN TESTS	TREATMENT	TOP DOSE (PROTEIN UNITS)	CONSTITUTIONAL REACTIONS AFTER INJECTION	FINAL SKIN TESTS	SERUM TAKEN
			TYPE	ONSET						
1	M	1912	R[1]	1936	R1,000—Mkd.[2]	P[3] Oct., 1936-38	10,000	1	R1,000—Mod.[4]	6/20/38
2	F	1907	R	1930	R100—Mkd.+	S[5] 1936-38	14,000	0	R100—Mod.	9/ 9/38
3	F	1906	R	1934	R10—Mkd.	S 1936 (Acetyl); P 1937-38	10,000	0	R10—Slt.[6]	9/15/38
4	M	1908	R	1932	R100—Mkd.	P 1935-36; no treatment 1937-38	10,000	0	R100—Mod.+	9/10/36
5	F	1891	R	1931	R10—Mkd.	P 1936-38	10,000	0	R100—Slt.	9/16/38
6	M	1892	R	1931	R100—Mkd.	P 1936-38	10,000	0	R100—Mod.+	11/ 1/38
7	F	1904	R	1931	R10—Mkd.	P 1936-38	10,000	1	R100—Slt.	8/19/38
8	M	1895	R	1933	R1,000—Mkd.	P 1935-38	10,000	0	R100—Mod.+	9/20/38
9	M	1925	R	1929	R100—Mkd.+	S 1935-38	3,000	0	R100—Mod.+	9/23/38
10	M	1893	R	1931	R1,000—Mkd.	S 1933-34; P 1935-37	10,000	0	R1,000—Mkd.	1/24/38
11	M	1893	R	1921	R100—Mkd.	S 1929; P 1933-38	7,000	2	R100—Mod.	4/ 5/38
12	F	1901	R	1928	R1,000—Mod.	S 1933-34; P 1935-38	15,000	0	R10,000—Neg.	5/27/38
13	F	1905	R	1929	R1,000—Mkd.	S 1932; P 1933-37	10,000	0	R1,000—Mod.+	6/14/38
14	M	1906	R	1917	R0.001—Mkd.	S 1930-31; P 1932-35	12,000	0	R100—Mkd.	6/16/36
15	M	1883	R	1918	R0.001—Mkd.-	P 1932-38	20,000	2	R100—Mkd.	5/ 4/38
16	M	1902	G[7]	1917	T[8]0.01—Mkd.	P 1932-38	16,000	0	T1,000—Mod.	3/31/38
17	M	1902	R	1931	R0.001—Mkd.	P 1932-38	16,000	0	R1,000—Slt.	3/31/38
18	F	1881	R	1914	R0.01—Mkd.	P 1931-38	10,000	1	R1,000—Mod.	5/13/38
19	M	1894	R	1922	R0.01—Mkd.	S 1928-29; S 1934-38	10,000	0	R1,000—Mod.+	5/23/38
20	M	1878	R	1930	R0.01—Mkd.	S 1932-38	10,000	0	R1,000—Mod.	9/16/38
21	M	1884	R	1900	R0.05—Mkd.	S 1931; P 1932-37	20,000	0	R10,000—Neg.	11/16/36
22	M	1888	R	1919	R0.01—Mod.+	S 1929-35; S 1937; no treatment 1936 or 1938	20,000	0	R1,000—Mod.	6/10/38
23	M	1870	R	1904	R0.01—Mkd.	S 1924-28; P 1936-38	5,000	0	R1,000—Mod.+	4/ 4/38

[1]R=Ragweed
[2]Mkd.=Marked reaction
[3]P=Perennial
[4]Mod.=Moderate reaction
[5]S=Seasonal
[6]Slt.=Slight reaction
[7]G=Grass
[8]T=Timothy

TABLE I—CONT'D

24	M	1904	R		R0.01—Mkd.	S 1931-38	6,000	0	R1,000—Mkd.	4/14/38
25	F	1893	R	1910	R0.01—Mkd.	S 1917-19; S 1927; S 1931-32; P 1933-34	8,000	1	R1,000—Mod.	5/12/38
26	M	1897	R	1905	R0.001—Mkd.	S 1930-35; P 1935-36; S 1937-38	7,500	1	R100—Mod.	3/25/38
27	M	1878	G	1930	T0.001—Mkd. +	P 1928-38	4,000	2	T1,000—Slt.	4/28/38
28	M	1909	R	1924	R0.01—Mkd.	S 1927-31; P 1934-38	10,000	0	R1,000—Slt.	12/17/38
29	M	1902	R	1918	R0.001—Mkd.	S 1928-38	10,000	0	R1,000—Mkd.	3/31/38
30	M	1892	R	1922	R0.001—Mkd.	S 1929-38	10,000	0	R100—Mod.	3/31/38
31	F	1885	R	1920	R0.0001—Mkd.	S 1923-32; no treatment since	10,000	0	R1,000—Mkd.	6/ 9/37
32	M	1888	R	1924	R0.001—Mkd.	S 1928-35; P 1935-37; S 1938	7,000	0	R1,000—Mod.	9/ 9/38
33	F	1907	G	1917	T0.05—Mkd.	S 1920-34; no treatment 1934-37	0.04x[9]	2	T1,000—Mkd.	7/19/37
34	F	1907	R	1920	R0.05—Mkd.	S 1920-34; no treatment 1934-37	0.05x	2	R1,000—Mkd.	7/19/37
35	M	1900	R	1926	R0.0001—Mkd.	S 1928-38	17,000	0	R10—Mkd.	9/ 9/38
36	M	1893	G	1908	T0.01—Mkd.	S 1918-21; S 1929-31; P 1932-38	8,000	3	T1,000—Slt.	6/ 3/38
37	F	1897	R	1921	R0.005—Mkd.	S 1925-26; P 1927-36	10,000	0	R1,000—Mod.	6/23/38
38	F	1881	G		T0.01—Mkd.	S 1924-32; P 1933-37	12,000	1	T,1000—Mod.	3/19/38
39	F	1915	R	1920	R0.001—Mkd.	S 1926-31; P 1931-38	20,000	0	R1,000—Mod.	6/27/38
40	M	1891	G	1921	T0.001—Mod.	S 1924-26; S 1929-33; P 1933-36; P 1937-38	2,000	0	T100—Mod.	7/ 7/36
41	M	1897	R	1899	R0.001—Mkd.	P 1925-38	15,000	0	R1,000—Mod. +	5/ 4/38
42	M	1895	R	1918	R0.0001—Mkd.	S 1926-32; P 1932-36	10,000	0	R1,000—Mkd.	12/20/37
43	M	1891	G	1929	T0.01—Mkd.	P 1924-38	20,000	0	T5,000—Slt.	2/ 4/38
44	M	1891	R	1902	R0.01—Mkd.	P 1925-37	20,000	1	R5,000—Slt.	2/ 4/38
45	M	1882	R	1923	R0.001—Mkd.	P 1925-38	20,000	0	R1,000—Slt.	4/22/38
46	F	1891	R	1919	R0.005—Mkd.	S 1923-33; P 1934-38	10,000	0	R1,000—Mod.	4/ 8/38
47	F	1889	R	1919	R0.005—Mkd.	S 1924-38	10,000	0	R100—Mkd.	9/15/38
48	F	1892	R	1922	R0.01—Mkd.	S 1924-30, P 1931-38	10,000	0	R1,000—Mod.	1/ 4/38
49	M	1876	R	1906	R0.001—Mkd.	S 1924-38	4,000	1	R100—Mod.	5/12/38
50	F	1895	G	1913	T0.01—Mkd. +	S 1923-25; P 1925-28; S 1929-38	17,000	0	T1,000—Slt.	4/14/38
51	M	1893	R	1898	R0.0001—Mkd.-	S 1924-26; P 1926-38	10,000	3	R1,000—Mod. +	5/13/38
52	M		R	1911	R0.001—Mkd.	S 1921-31; P 1932-38	20,000	0	R1,000—Slt.	6/ 2/38
53	M	1863	G	1873	T0.05—Mkd.	S 1917-27; P 1927-36	16,000	0	T5,000—Mod.	3/31/38
54	M		R	1900	R0.2—Mkd.	S 1915-37	1,600	18	R100—Mkd.	5/27/38
55	M	1884	G	1904	T0.01—Mkd.	S 1915-38	1,750	10	T1,000—Mkd.	5/ 3/38

[9]x=Total nitrogen

TABLE IA

CLINICAL AND SEROLOGIC DATA ON UNTREATED CONTROL GROUP

PATIENT	SEX	HAY FEVER		AGE	SKIN TESTS	SERUM DILUTION TRANSFERING	POLLEN EXTRACT NEUTRALIZING (UNITS PER C.C.)
		DURATION (YEARS)	TYPE				
A. S. A.	M	1	R*	24	R1,000 Mkd.†	1:100	10-30
E. Z. N.	F	2	R	34	R1,000 Mkd.	1:100	30-100
H. P. R.	F	2	R	30	R10 Mkd.	1:100	30-100
H. G. Z.	M	2	R	50	R1,000 Mkd. +	1:1,000	30-100
J. S. N.	M	2	R	47	R100 Mkd.	1:100	30-100
G. B. K.	M	3	R	40	R10 Mkd.	1:100	30-100
C. E. N.	F	3	R	38	R1,000 Mkd.	1:100	30-100
G. L. N.	M	3	R	27	R100 Mkd.	1:1,000	100-300
S. S. R.	M	3	R	46	R100 Mkd.	1:100	30-100
J. B. Y.	F	4	R	36	R1,000 Mkd. +	1:1,000	100-300
L. C. T.	F	4	R	22	R1,000 Mkd.	1:100	100-300
A. A. O.	M	4	R	28	R1,000 Mkd.	1:100	10-30
B. B. N.	F	4	R	38	R100 Mkd.	1:100	100-300
M. F. R.	M	5	R	59	R100 Mkd.	1:1,000	30-100
N. D. H.	F	5	R	45	R10 Mkd.	1:100	10-30
M. E. S.	F	5	R	32	R10 Mkd.	1:100	30-100
B. C. O.	F	5	R	33	R100 Mkd.+	1:1,000	30-100
S. M. A.	M	5	R	50	R10 Mkd.	1:1,000	300-1,000
F. T. R.	F	6	R	29	R100 Mkd. +	1:10	30-100
D. H. R.	M	6	R	37	R100 Mkd.	1:100	30-100
S. B. R.	F	7	R	41	R100 Mkd.	1:100	100-300
M. P. Z.	M	7	R	28	R1,000 Mkd. +	1:100	10-30
R. S. T.	M	8	R	36	R100 Mkd.	1:100	100-300
E. C. N.	F	10	R	37	R100 Mkd.	1:1,000	300-1,000
P. D. K.	M	10	R	33	R100 Mkd.	1:100	10-30
A. H. S.	M	12	R	23	R10 Mkd.	1:100	300-1,000
J. L. W.	F	12	R	44	R100 Mkd.	1:100	30-100
J. H. H.	M	13	R	20	R1,000 Mkd.	1:100	100-300
J. C. Z.	F	14	R	52	R1,000 Mkd.	1:1,000	100-300
J. B. H.	M	15	R	55	R10 Mkd.	1:100	30-100
D. G. T.	F	20	R	50	R1,000 Mkd. +	1:100	100-300

*R=Ragweed
†Mkd.=Marked reaction.

four classes: those showing little or no change in skin reaction; those showing a definite but moderate decrease in reaction during treatment; those showing a marked decrease in reaction; and those in which the reaction to intracutaneous tests disappeared. In no case was the skin reaction definitely greater after than before treatment.

TABLE II

CHANGES IN SKIN TESTS DURING TREATMENT

YEARS OF TREATMENT	CASES SHOWING LITTLE OR NO CHANGE	CASES SHOWING MODERATE DECREASE	CASES SHOWING MARKED DECREASE	CASES IN WHICH FINAL TESTS WERE NEGATIVE
Less than 5	0	6	2	0
5 to 9	5	8	3	2
10 to 14	4	5	10	0
15 or more	2	3	5	0
Total	11	22	20	2

Forty-four of these fifty-five long treated cases showed a definite decrease in the skin reactions. In only two cases were the intra-

cutaneous tests negative after treatment. Within the limits covered by the group there was no evident correlation between the duration of treatment and amount of change in the tests. Neither of the two cases treated longest (twenty-three years) showed a definite decrease in the skin reactions, possibly because both had relatively low doses of pollen extract.

Dilution Tests.—The skin-sensitizing capacity of the serum of each patient in Group 1 was determined by the dilution method.[15] Serum was diluted 1:10, 1:100, and 1:1,000 with 0.9 per cent sodium chloride solution. One-tenth cubic centimeter of each dilution and of the concentrated serum was injected into the skin of the back of a normal nonallergic test subject who gave negative reactions to intracutaneous tests with timothy and ragweed pollen extracts. The sites were tested two days later with 0.025 c.c. of pollen extract, 1,000 protein units per cubic centimeter. Sera of grass-sensitive cases were tested with timothy pollen extract, and those of ragweed cases with low ragweed pollen extract. The reactions were recorded (± to ++++) on the same scale used by Cooke and co-workers.[1]

It has been noted frequently that the skins of various normal individuals differ in the intensity of their reactions when sensitized with the same serum. Therefore, it is much more difficult to determine an absolute end point in dilution test of one serum than to establish relative values for two sera in the same test subject. Since the present investigation required the measurement of absolute end points, subjects for dilution tests were carefully chosen from those previously shown to give good reactions on passive transfer. As a further test of the reactivity of the skin of the subject, dilutions of a known serum were included in each experiment. Dilution and neutralization tests were not done on the same subject in order to avoid the possibility that sites made with diluted serum might be affected by pollen extract absorbed into the circulation.[16]

The results of dilution tests are shown in Table III. The skin-sensitizing capacity of sera of Group 1 varied widely, from nine sera which failed to sensitize normal skin to three which transferred passive sensitivity in dilutions of 1:1,000. The distribution of cases in groups according to duration of treatment and the highest dilution producing passive sensitization is summarized in Table IV. For comparison with the sera of the treated cases, the results of similar dilution tests on sera of the untreated control group are also included in this table. The results of dilution tests on each case of the control group were shown in Table IA. There was no correlation between the antibody titer and either the duration of hay fever or the age of the patient in this group.

As shown in Table IV, the sera of the treated group did not transfer sensitivity in such high dilutions as the untreated group. Nine of the fifty-five treated cases failed to sensitize normal skin, while thirty more cases transferred only in dilutions of 1:10 or less.

TABLE III

RESULTS OF DILUTION AND NEUTRALIZATION TESTS ON SERA OF GROUP 1

NO.	TYPE OF HAY FEVER	YEARS OF TREATMENT	DILUTION TEST				NEUTRALIZATION TESTS WITH POLLEN EXTRACT UNITS PER C.C.						
			CONCENTRATED	1:10	1:100	1:1,000	10	30	100	300	1,000	2,000	5,000
1	R*	2		+	+	0				+	±	0	
2	R	3	+++	++	±				++	+	+		
3	R	3		+	±	0			++	+	+	±	
4	R	3		+++	++	+				++	+	0	
5	R	3		++	±	0			+	±	0		
6	R	3		+++	++	+				++	+	+	±
7	R	3		+	0	0			++	+	0		
8	R	4		++	0	0			+++	±	0		
9	R	4		+++	+	0			+++	++	+		
10	R	5	+++	++	0		++		++	0			
11	R	5		+++	++	0			+++		+	+	0
12	R	6	0										
13	R	6	+++	+	0	0	+++		++	0	0		
14	R	6	+++	+++	+	0			+++		++	+	0
15	R	6	+++	++	0				++	±	0	0	
16	G†	7	++++	+++	++	0			+++	++	0		
17	R	7	++++	+++	++	0			+++		+	+	
18	R	7	++	++	0				++	++	+	0	
19	R	7	++	+	0		+		±		0		
20	R	7		+	0	0	++		+	0	0		
21	R	7	0										
22	R	8	++	±	0			+	±	0			
23	R	8		++	+	0			++	++	+	+	+
24	R	8	+++	+	0				+	0	0		
25	R	8	+	0			+	±	0				

*R=Ragweed
†G=Grass

TABLE III—CONT'D

26	R	9	+++	+	0	0	+++	+	0				
27	G	10	++	±	0		+	0	0				
28	R	10	+++	+	0				++	±	0		
29	R	10	++	±	0		++	+	±	0	0		
30	R	10	++	0	0		++	+	0				
31	R	10	+++	++	0		++		±		0		
32	R	11		++	+	0		+++	+++	++	0		
33	G	11	++	+	0		+	+	0				
34	R	11	+	0	0		++	+	0				
35	R	11		++++	+++	+			++++	++++	+++	+++	
36	G	12	0										
37	R	12	0										
38	G	13	0										
39	R	13	+++	++	+				+++	++	±		
40	G	13	±	0			±		0				
41	R	13	+++	+++	+	0	+++		+++	+	0		
42	R	13	++	+			++		+	0	0		
43	G	13	0										
44	R	13	0										
45	R	14	+++	+	0				++	+	+		
46	R	15	++	±	0		++		+	0	0		
47	R	15		+	0	0		++	++	±	0		
48	R	15	++	+	0		++		±		0		
49	R	15	++	+	0	0	+++		++	+	+		
50	G	16	++	±	0		++	+	0				
51	R	16	+++	++	0		+++		+	0	0		
52	R	18	++	+	0				++	+	0		
53	G	20	0										
54	R	23	++	+	0			+	0				
55	G	23	0										

Sera of cases treated less than five years had nearly the same skin-sensitizing capacity as the sera of untreated cases. The changes occurring during this stage of treatment are more clearly shown in the study of Group 2 (Table VIII) in which the sera of the same patients, taken before and after treatment, are compared.

TABLE IV

RELATION OF HIGHEST DILUTION TRANSFERRING AND DURATION OF TREATMENT

YEARS OF TREATMENT	SERA NOT TRANSFERRING	SERA TRANSFERRING IN DILUTIONS				TOTAL CASES
		CONCENTRATED	1:10	1:100	1:1,000	
Less than 5	0	0	2	5	2	9
5 to 9	2	1	9	5	0	17
10 to 14	5	3	7	3	1	19
15 or more	2	0	8	0	0	10
Total of treated cases	9	4	26	13	3	55
Untreated cases	0	0	1	22	8	31

In patients with periods of treatment longer than five years, there was evidence of a progressive loss of skin-sensitizing antibody. Of twenty-nine patients treated for more than ten years, seven showed no skin-sensitizing activity, and eighteen others showed a marked decrease of antibody by passive transfer test. However, even in the group treated more than fifteen years, sera of eight of ten patients still sensitized normal skin.

Neutralization Tests.—On those sera of Group 1 which showed evidence of the skin-sensitizing antibody, neutralization tests[17] with the corresponding pollen extracts were carried out according to the quantitative technique used in previous work at this clinic.[1] Mixtures of serum with equal volumes of pollen extracts of various strengths were made, using timothy pollen extract in cases sensitive to grasses and low ragweed pollen extract in those sensitive to ragweed. The pollen extracts were kept sterile at 7° C. and used only within three weeks of the date of preparation. Sites were prepared by the injection into the skin of a normal test subject of 0.1 c.c. of each of these mixtures and of a control mixture of serum and 0.9 per cent sodium chloride solution. These sites were tested two days later by the injection into each site of 0.025 c.c. of a dilution of 1,000 units per cubic centimeter of the same pollen extract used in making the mixture.

In previous work the mixtures of serum and pollen extract were kept overnight in the refrigerator before injection into the test subject. It was found that this step was not essential, and it was, therefore, omitted. The same modification has been suggested by Langner and Kern.[3]

In recording the results of neutralization tests, we have omitted entirely the immediate reactions to the mixtures at the time of making the sites and considered only the reactions obtained on testing two

days later with pollen extract. While the immediate reactions were of theoretical interest as a clue to the mechanism of the "blocking" of neutralization in treated sera,[1] from the practical standpoint they were much less definite and more difficult to evaluate than the reactions on subsequent testing with pollen extract. Many of the sera caused a definite reaction when injected into the skin in mixtures with an equal volume of saline. While this "irritative" reaction in the control site was usually less marked than the reactions in sites made with mixtures of serum and pollen extracts, and faded sooner, it made the reading of the immediate reactions very difficult.

It was found that the amount of pollen extract required to neutralize the skin-sensitizing activity of each serum was practically constant when tested on different test subjects. Care was taken not to use mixtures containing very strong pollen extract when other sites on the same test subject contained serum which transferred very poorly. This minimized errors due to pollen extract absorbed into the circulation.[16]

The results of the neutralization tests are shown in detail in Table III and summarized in Table V. For comparison with the sera of the treated cases, the results of similar neutralization tests on sera of the untreated control group are also included in Table V. Twenty-eight of these thirty-one sera were neutralized by 300 or less units of pollen extract per cubic centimeter.

TABLE V

RELATION OF NEUTRALIZATION TEST TO DURATION OF TREATMENT

YEARS OF TREATMENT	UNITS OF POLLEN EXTRACT TO NEUTRALIZE 1 C.C. OF SERUM					TOTAL NUMBER OF CASES
	0-30	30-100	100-300	300-1,000	1,000+	
Less than 5	0	0	2	2	5	9
5 to 9	1	3	5	1	5	15
10 to 14	2	5	2	3	2	14
15 or more	0	3	3	1	1	8
Untreated cases	5	14	9	3	0	31

Most of the cases treated three to five years showed high neutralization points as might be expected to result from the presence of a large amount of "blocking" antibody. However, fifteen of the twenty-two sera of cases treated for ten or more years were neutralized by 300 units of pollen extract per cubic centimeter, and ten by 100 units or less. These figures were not only much lower than the neutralization points found by Cooke, Barnard, Hebald and Stull[1] for sera of cases treated one year, but were even comparable to the values found for sera of typical hay fever cases taken before treatment. The treated sera which were neutralized by very small amounts of pollen extract were found to be, in general, those which transferred sensitivity poorly.

In Table VI the sera are grouped according to the highest dilution

in which they transferred sensitivity and the amount of pollen extract neutralizing the transfer reaction. In compiling this table, mixtures of pollen extract and serum showing questionable (±) reactions were considered as representing the neutralization point. All of the sera which transferred sensitivity only in concentrated form were neutralized by 100 or less units of pollen extract per cubic centimeter. Twenty of the twenty-six sera transferring in dilutions of 1:10 were neutralized by 30 to 300 units. Of thirteen sera transferring in dilutions of 1:100, twelve required more than 300 units for neutralization, while the three sera transferring in 1:1,000 dilutions all required more than 1,000 units. From these results it was apparent that the amounts of pollen extract needed to neutralize the sera of these long treated cases were roughly proportional to the amount of skin-sensitizing antibody present. This relationship was not evident in the cases studied before treatment or during the first year of treatment by Cooke and co-workers[1] or by Harley.[2]

TABLE VI

HIGHEST DILUTION IN WHICH SERUM SENSITIZED SKIN	UNITS OF POLLEN EXTRACT REQUIRED TO NEUTRALIZE 1 C.C. OF SERUM						
	0-10	10-30	30-100	100-300	300-1,000	1,000-2,000	2,000+
Concentrated	1	1	2				
1:10		1	9	11	2	3	
1:100				1	4	4	4
1:1,000						1	2

Inhibition Tests.—The sera which did not sensitize even in concentrated form were tested for blocking or inhibition of neutralization by a method similar to that used by Cooke, Loveless, and Stull.[5] The sera to be tested were mixed with equal volumes of serum from an untreated patient acutely sensitive to the same pollen, and similar control mixtures were made of normal (nonallergic) human serum and serum of the same untreated pollen-sensitive patient. These mixtures, which then sensitized normal skin, were compared in neutralization tests carried out as described above. If the mixture containing the treated serum required for neutralization an amount of pollen extract definitely higher than that which neutralized the control mixtures, the serum was considered to contain the blocking antibody.

Walzer[18] has suggested that the blocking antibody is precipitin present in amounts too small to be detected by the methods used by Cooke and by Harley. Since neutralization apparently involves a reaction between skin-sensitizing antibody and antigen, any antibody which combined with the specific reacting groups of the antigen would produce blocking. The use of the term "blocking" antibody does not imply that this is different from other antibodies, but simply refers to the only means by which its presence has yet been detected.

In a few cases the mixtures of treated and untreated sera were diluted 1:2 or 1:5 before neutralization. In these cases the normal control serum was diluted in the same manner.

TABLE VII

INHIBITION TESTS

Ragweed Cases

SERUM OF CASE	MIXED WITH SENSITIVE SERUM	NEUTRALIZATION OF MIXTURE WITH LOW RAGWEED UNITS PER C.C.					
		10	25	50	100	150	200
43	H. O. R.			++	+	0	0
12A	H. O. R.			+	+	0	0
N_1*	H. O. R.			+	+	0	0
N_2	H. O. R.			+	±	0	0
N_3	H. O. R.			+	+	0	0
N_4	H. O. R.			+	0	0	0
37	H. O. R.			++	±	0	0
37A	H. O. R.			+	±	0	0
37B	H. O. R.			++	±	0	0
12	H. O. R.			++	±	0	0
12A	H. O. R.			++	±	0	0
N_4	H. O. R.			?	±	0	0
25B	H. O. R.		+++	+	±		0
N_5	H. O. R.		+++	++	±		0
21 (1-5)	H. O. R. (1-5)	+	±	0			
N_5 (1-5)	H. O. R. (1-5)	+	±	0			
25 (1-2)	H. O. R. (1-2)		+	±	0		
25A (1-2)	H. O. R. (1-2)		+	±	0		
N_5 (1-2)	H. O. R. (1-2)		++	±	0		

Timothy Cases

		NEUTRALIZATION OF MIXTURE WITH TIMOTHY UNITS PER C.C.					
		25	50	100	150	200	300
38	S. C. I.		+++	++		±	0
53	S. C. I.		+++	±		0	
N_5	S. C. I.	++	+	0			
44	W. E. S.		++++	±	±?	0	
36	W. E. S.		++++	+	+	0	
N_2	W. E. S.		++++	±	0	0	
55	W. E. S.		+++	+	0	0	
53	W. E. S.		+++	++	+	0	
N_5	W. E. S.		+++	±	0	0	

*N_1 to N_5=Normal sera.

The same untreated ragweed-sensitive serum (H.O.R.) was used for all the tests on cases of ragweed hay fever; two different timothy-sensitive sera (S.C.I. and W.E.S.) were used. Five different normal (r. nallergic) sera were used as controls. When two or more of these normal controls were used simultaneously on the same test subject, *slight* differences were occasionally noted (Table VII). These variations were considered in judging the significance of the inhibition of neutralization by sera of treated hay fever cases.

Sera of nine patients were studied by this method. One of these had been treated for both grass and ragweed hay fever. These sensitivities

were considered separately so that there were five cases of ragweed hay fever and the same number due to grass pollen. Serum was obtained from three of these patients in two or more different years. These sera have been listed in the table under the number of the case and distinguished by the letters A and B. Sera obtained from Case 25 in 1936 and 1937 did not passively transfer skin sensitivity and were included in this group. Serum obtained from the same patient in 1938 transferred sensitivity slightly, and this was indicated in Table III.

The results of the inhibition tests are shown in Table VII. The changes in neutralization produced by the admixture of treated sera were comparatively small. The tests on each serum were checked in other test subjects with similar findings. In three cases (53, 38, and 36) there was definite evidence of inhibition; in one case (44) there was a suggestion of such activity, and in six cases, negative results.

There was an interesting difference between the ragweed and grass pollen groups; three of the five cases of grass hay fever showed definite and one showed suggestive evidence of inhibiting activity, while none of the ragweed hay fever cases showed such activity. Three of the sera (Cases 36, 44, and 53) which showed evidence of blocking activity were tested for precipitins. The results were negative, in accordance with the findings of previous workers.[1, 2, 5]

GROUP 2

Since the cases of Group 1 which had been treated over a period of years showed serologic results quite different from those noted after treatment for one year, it seems worth while to record the changes observed in the sera of eight cases during the course of treatment over periods of from three to five years. In these cases serum was studied before treatment was started and at various intervals during the course of injections, so that the observations cover the intermediate period between the early stage of treatment studied by Cooke, Barnard, Hebald, and Stull[1] and the later stages included in Group 1.

The sera of patients in this group were collected over a period of five years. Dilution and neutralization tests on each specimen were done after the serum was taken, and the remainder of each serum was kept sterile in a rubber-capped vial at 7° C. When the dilution and neutralization tests were repeated with the same sample of serum after from three to five years, there was no evidence of deterioration of the antibody, such as has been reported by Langner and Kern.[3] Therefore, all of the sera collected from each patient were compared in dilution tests on the same test subject and compared in neutralization on another test subject.

Dilution Tests.—The results of the dilution and neutralization tests on these cases are shown in Table VIII. In order to show more clearly the changes in the amount of skin-sensitizing antibody, dilution tests

TABLE VIII

RESULTS OF DILUTION AND NEUTRALIZATION TESTS IN GROUP 2

CASE	SERUM TAKEN	DURATION OF TREAMENT	DILUTION TESTS						NEUTRALIZATION TESTS (LOW RAGWEED UNITS PER C.C.)						
			1:10	1:30	1:100	1:300	1:1,000	1:3,000	10	30	100	300	1,000	2,000	5,000
2	4/ 7/36	0			++	±	0		+++	±	0				
	9/ 8/36	5 mo.		+++	++	+	0					++	+	±	
	9/16/38	3 seasons		++	+	0					++	+	+		
6	7/23/36	0			++	+	0	0		+	±	0			
	9/29/36	2 mo.			+++	+++	++	±					+	±	0
	11/ 1/38	27 mo.			++	+	0	0				++	+	+	±
11	8/11/33	0			+++	+	0			+	+	0			
	10/23/34	12 mo.			+++	++	±				+++		+	0	
	4/ 5/38	53 mo.			++	+	0				+++		+	+	0
5	3/27/36	0			+	0	0			±	0				
	9/15/36	6 mo.			++	+	0				+	0	0		
	10/ 5/37	19 mo.			+	±	0				++	0	0		
	9/16/38	30 mo.		+	±	0	0				+	±	0		
1	10/ 3/36	0			+++	++	+				++	+	0		
	10/25/37	13 mo.			++	+	0					+++	++	0	
	6/20/38	21 mo.		++	+	0	0					+	±	0	
7	3/24/36	0		++	+	0				++	±	0			
	8/ 4/36	4 mo.		++	+	±	0				+++	++	±		
	8/19/38	28 mo.	+	±	0	0	0				+++	+	0		
4	5/20/35	0			+++	++	+	0		+++	++	0			
	8/26/35	3 mo.			+++	++	+	0			+++	±	0		
	1/ 6/36	4 mo.			+++	++	+	0				+	0	0	
	9/10/36	9 mo.			++	+	0	0				++	+	0	
	7/14/38	No treatment after 4/12/37			++	+	0	0				+	0	0	
3	4/20/36	0		±	±	0				+	0				
	8/10/36	4 mo.		+	±	0					±	0	0		
	9/15/38	16 mo.		+	+	0					++	+	+	±	

were made with dilutions of 1:10, 1:30, 1:100, 1:300, 1:1,000 and 1:3,000.

Cases 2, 6, 11, 5, 1, and 7 were treated regularly with good symptomatic results. Case 4 was treated with good results in 1935 and 1936, when he stopped treatment, and he had a return of symptoms in 1938. Case 3 was treated in 1936 with a low ragweed extract acetylated with ketene.[19] This extract, which has since been discarded as worthless, produced no definite change in symptoms. In 1937 and 1938 Case 3 was treated with regular extract with excellent results. It will be noted that the serum taken Aug. 10, 1936, shows no definite serologic change as a result of treatment, while that taken Sept. 15, 1938, shows a typical response. The serum taken after treatment with acetylated extract, although shown in Table VIII, is not included in the summary of results.

In five cases serum was taken after from two to five months of treatment. In four of these, there was a slight or definite increase in the amount of skin-sensitizing antibody as shown by the dilution tests; in Case 4 there was no change. Case 6 showed a very marked increase of antibody during the first two months of injection treatment. With further treatment, all cases showed a drop in the amount of skin-sensitizing antibody. At the end of from two to five years of treatment, five of the seven cases showed less antibody than before treatment. The other two cases, which had shown an increase of antibody early in the treatment, returned to their original levels.

Neutralization Tests.—The amount of pollen extract required to neutralize the skin-sensitizing capacity of the serum was, in every case, increased during the first year of treatment. In five patients the neutralization value remained the same or showed a further rise during one to three subsequent years of treatment, despite a drop in the amount of antibody as measured by the dilution test. The sera obtained from Cases 5 and 6 at the end of two and one-half years of treatment were neutralized by smaller amounts of pollen extract than were required by sera taken earlier in the course of treatment. These sera also showed a definite decrease in the amount of antibody as measured by the dilution test and may represent the beginning of the decrease in the amount of antibody and neutralization value which was apparent in patients of Group 1 treated over longer periods.

In contrast to the cases which were treated regularly with good results, Case 4 illustrated the changes which occurred when treatment was stopped and hay fever recurred. In 1936, he was treated successfully, and the serum showed an increase in neutralization value, accompanied by a drop in the amount of antibody as measured by the dilution test. The serum obtained in 1938, seventeen months after treatment was stopped and when hay fever symptoms were returning, showed a lower neutralization value and no change in the titer by dilution test.

DISCUSSION

The data presented are not as complete as might be desired in that no one case has been studied through all stages of treatment. However, until such a series of observations are collected over a period of years, these studies may be useful as a clue to the sequence of serologic changes in hay fever cases treated for a long time.

The amount of skin-sensitizing antibody, as measured by the dilution test, in most cases was increased during the first two to five months of treatment. This is shown in the studies of Group 2 and has been confirmed by unpublished data on other cases at this clinic. As treatment was continued, the antibody titer decreased. This decrease was apparent in most of the cases of Group 2 during the second and third years of treatment, and the results of Group 1 indicated that the decrease of antibody was progressive until a considerable number of sera did not transfer skin sensitivity after from ten to fifteen years of treatment.

Consideration of the changes of antibody content of sera in Group 2 may account for some of the conflicting reports of previous writers. Levine and Coca[10] and Gay and Chant,[11] studying patients treated from two to three months, found the amount of antibody to be unchanged or increased. Cooke and co-workers[1] treated their cases with somewhat higher doses over periods averaging twelve months, and it is probable that many had passed their highest level of antibody content before the second serum was taken, so that the changes were not striking. Of their eight cases, three showed an increase of antibody, one a slight decrease, and four no definite change. Harley[2, 8] reported a decrease in skin-sensitizing antibody during the first few months of treatment. His patients received injections from three to five or more times a week, instead of once a week as in the present series, and the doses were apparently two or three times as large. This more intensive treatment may have brought the cases sooner to the stage of decreasing antibody content.

The amount of pollen extract required to neutralize the serum increased during the first season of treatment in every patient. In most patients of Group 2, the neutralization point of the serum was even greater after two or three seasons of treatment. However, the patients of Group 1 treated longer than five years showed decreases in the amount of pollen extract needed for neutralization roughly parallel to the fall of the amount of antibody as measured by the dilution test. Two of the patients of Group 2 (Cases 1 and 7) showed evidence of the beginning of such a drop in neutralization value after from two to three years of treatment.

From the study of the dilution and neutralization reactions of the serum during the early stages (first three to four months) of treatment when both values are increasing, or after five years of treatment

when both are decreasing, it might be thought that the changes in the antibody were purely quantitative and that the assumption of the presence of a blocking or inhibiting antibody was superfluous. This was implied by Schmidt and Lippard[4] in using the neutralization reaction as a measure of the amount of antibody in sera of hay fever patients during treatment.

However, the sera of patients in Group 2 followed over from two to five years of treatment invariably showed, at some stage, changes in the neutralization point which were not paralleled by corresponding changes in the dilution titer (Table VIII). In four of seven cases there were periods during which the neutralization point rose while the dilution test showed a definite decrease in the amount of skin-sensitizing antibody. When the sera of Case 6, obtained before and after twenty-eight months of treatment, were compared in dilution tests, there was apparently the same amount of sensitizing antibody. When the same two sera were compared in neutralization tests, however, there was evidence of a fifty fold change. Likewise, the serum of Case 11, taken before and after fifty-six months of treatment, gave the same result on dilution test, but showed a twenty fold increase in neutralization value. These results could scarcely be explained except on the basis of a qualitative change in the antibody of the serum.

The dilution test is a measure of the amount and activity of skin-sensitizing antibody in a serum, while the neutralization value might be expected to be influenced not only by the amount of skin-sensitizing antibody, but also by the presence of any other antibody or substance which combined with the antigen either in the test tube or after injection into the skin. The changes in neutralization value during treatment, which are not paralleled by changes in the dilution titer, might be due to formation of antibody less active in skin sensitization than that present before treatment. The blocking antibody described by Cooke, Loveless, and Stull[5] in nonallergic subjects had no demonstrable skin-sensitizing activity. The changes observed in the serum of hay fever cases during treatment might be due either to the formation of such an antibody entirely distinct from the sensitizing antibody or to the formation of skin-sensitizing antibody of lessened "avidity." Although the present data do not offer grounds for excluding either hypothesis, the fact that the dilution test shows an increase of skin-sensitizing antibody during the first few months of treatment gives some basis for the latter hypothesis.

Of the ten cases in which the serum no longer passively sensitized normal skin, three showed definite and one suggestive evidence of blocking antibody. However, the amount of such activity shown by the sera of the present series was small, even where definite. Admixture of the treated sera with untreated hay fever serum in no case produced a change of neutralization comparable to the change produced

by even three months of treatment. None of the sera showed inhibiting activity as great as that reported by Cooke, Loveless, and Stull.[5] This difference was probably due to the fact that none of these patients received doses even half as large as were given to the nonallergic persons in that experiment.

While the inhibiting activity apparently depends upon the presence of an antibody produced in response to pollen injections, its importance in the protection conferred by such treatment is doubtful. It cannot be considered the only essential factor, since six of the sera tested showed no evidence of such activity. The failure of this group of sera to sensitize skin was due to a loss of skin-sensitizing antibody and not to the presence of an inhibiting substance.

On the other hand, desensitization through decrease of antibody cannot be considered the only mechanism of protection. The increase of antibody in the early stages of treatment suggests an analogy to the condition of antianaphylaxis in experimental animals, where an increase of circulating antibody protects against anaphylactic shock.[20] However, since the antibody present in the serum of treated hay fever patients does not precipitate or inactivate the pollen antigen,[1] the two phenomena cannot be considered identical. The relative importance of the changes in the amount and kind of antibody in regard to clinical protection at various stages of treatment can be established only by further study. However, it must be borne in mind that cellular antibody is probably more directly concerned than that of the blood.

SUMMARY

1. Sera of fifty-five cases of hay fever, after successful injection treatment over periods of from two to twenty-three years, have been studied by the methods of dilution and neutralization. Sera of eight cases have been studied at various stages of treatment over periods of from two to five years.

2. The amount of skin-sensitizing antibody, measured by the dilution test, was found to increase during the first few months of treatment and then subsequently to decrease. After from ten to twenty-three years of treatment, seven of twenty-nine sera no longer passively sensitized human skin. Eighteen others showed a striking decrease in the amount of skin-sensitizing antibody.

3. The amount of pollen extract needed to neutralize the skin-sensitizing antibody of the serum was found to increase during the first two to five years of treatment and to decrease over succeeding years.

4. At certain stages of treatment, the changes in the neutralization point did not parallel the changes in the amount of antibody shown by the dilution test, and this suggested the occurrence of qualitative, as well as quantitative, changes in the antibody.

5. Sera of long treated cases which did not sensitize normal skin showed little or no inhibiting effect on the neutralization of sera of untreated hay fever patients.

6. In the majority of cases, the reactions to intracutaneous tests were definitely decreased after treatment, but the reactions became negative in only two of fifty-five cases.

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STUDIES IN ABSORPTION OF UNDIGESTED PROTEIN IN HUMAN BEINGS

VIII. Absorption From the Rectum and a Comparative Study of Absorption Following Oral, Duodenal, and Rectal Administrations

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IN PREVIOUS communications the results of studies on the absorption of undigested peanut protein following oral[1] and intraduodenal[2] administrations were reported. It was found that, following intraduodenal feeding, absorption of the peanut antigen was more rapid by several minutes than that following its oral consumption. It was also observed that, in the presence of gastric hyperacidity, the absorption of the antigen was retarded, while in hypoacidity it was accelerated. This obtained, not only following the oral intake of antigen, but even when it was administered directly into the duodenum. The present communication deals with the absorption of peanut antigen following its introduction into the rectum.

Sussman, Davidson, and Walzer[3] had at an earlier date studied the absorption of egg protein from the rectum in a small series of adults. They demonstrated that the direct technique for demonstrating the absorption of unaltered protein which had been employed with oral administration[4] could be satisfactorily applied in rectal studies. Smyth and Stallings[5] at a later date successfully used this technique in a similar study on infants and children.

The technique employed in the present study has been described in detail in previous communications and will be briefly summarized here. The subject to be studied was kept for forty-eight hours on a diet from which all nuts were carefully excluded. He was then passively locally sensitized to peanut by an intracutaneous injection of human serum obtained from a patient whose serum showed a high reagin titer for this antigen. Clinically this patient was extremely sensitive to peanut and showed a very marked cutaneous reaction to a skin test with it. One-twentieth cubic centimeter of a 1:10 dilution of this serum was injected intracutaneously in the forearm. On the following morning, without any special preliminary preparation of the subject, the peanut meal, consisting of 10 Gm. of raw ground peanuts in 20 c.c. of water, was introduced by tube into the rectum. The sensitized cutaneous site was then kept under observation. The onset of a

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reaction at this site, characterized by erythema, pruritus, and wheal formation, heralded the entrance of the peanut into the circulation. The interval between the introduction of the meal and the appearance of the erythema at the sensitized site was considered the absorption time for that person.

TABLE I

SUMMARY OF STUDIES ON RECTAL ABSORPTION OF PEANUT ANTIGEN
(THIRTY-ONE CASES)

CASE NO.	AGE	SEX	DIAGNOSIS	DEGREE OF GASTRIC ACIDITY	ABSORPTION TIME IN MINUTES	GROUP AVERAGE IN MINUTES
106	38	M	Cholelithiasis	Normal	32	
110	34	F	Cholecystitis	Normal	15	
113	21	M	Colitis (mucous)	Normal	17	
114	53	M	Gastric neurosis	Normal	16	
123	38	F	Chronic cholecystitis	Normal	13	18.6
101	27	M	Duodenal ulcer	Hyper.	14	
105	43	M	Gastric ulcer	Hyper.	14	
107	27	M	Colitis	Hyper.	26	
112	29	M	Duodenal ulcer	Hyper.	18	
115	61	F	Gastric neurosis	Hyper.	36	
117	37	M	Duodenal ulcer	Hyper.	16	
119	30	F	Chronic cholecystitis	Hyper.	18	
121	53	M	Duodenal ulcer	Hyper.	15	
122	40	M	Gastric neurosis	Hyper.	17	
126	49	M	Gastric ulcer	Hyper.	23	
127	30	M	Gastric neurosis	Hyper.	25	
128	31	F	Gastric ulcer	Hyper.	28	
129	48	M	Duodenal ulcer	Hyper.	28	21.4
102	37	F	Chronic cholecystitis	Hypo.	13	
103	56	F	Cholelithiasis	Hypo.	10	
104	39	F	Postoperative gall bladder disease	Hypo.	20	
108	53	F	Carcinomatous ulcer of stomach	Hypo.	22	
109	62	M	Visceroptosis	Hypo.	21	
111	30	F	Cholelithiasis	Hypo.	23	
116	56	M	Colitis	Hypo.	18	
118	23	F	Visceroptosis	Hypo.	13	
120	55	F	Postoperative gall bladder disease	Hypo.	19	
124	54	F	Chronic cholelithiasis	Hypo.	11	
125	46	M	Gastric neurosis	Hypo.	18	
130	56	F	Chronic cholecystitis	Hypo.	16	
131	30	F	Colitis	Hypo.	15	16.8
				Average for Entire Series		19.0

The subjects employed in this study were adults of both sexes, varying in age from 21 to 62 years, who suffered with various organic and functional disturbances of the gastrointestinal tract. The final diagnosis in each case, determined after careful investigation, is listed in Table I. As in previous studies, the cases were roughly divided into three groups according to the degree of gastric acidity. They were designated as cases with hyperacidity, normal acidity, or hypoacidity, according to the commonly accepted standards which were outlined in detail in previous communications.[1, 2] Atopic patients were excluded from the study.

Following rectal administration of the peanut meal, the absorption rates for the thirty-one cases in this series varied from 10 to 36 minutes. The average for the entire group was 19 minutes.

The results of the earlier studies[3] on egg absorption from the rectum had suggested that the rectal absorption rate might be influenced by the degree of gastric acidity. This impression was confirmed in the present study. It will be noted from the data presented in Table I that, in the five cases with normal acidity, the average absorption rate was 18.6 minutes. In the thirteen cases with hyperacidity, the average rate was 21.4 minutes, which was somewhat slower than the normal. For the thirteen cases with hypoacidity, the average absorption rate was 16.8, which was more rapid than the normal.

TABLE II

COMPARATIVE STUDY OF ABSORPTION RATES AFTER THE ORAL, DUODENAL, AND RECTAL ADMINISTRATIONS OF PEANUT PROTEIN IN FOURTEEN CASES

CASE NO.	AGE	SEX	DIAGNOSIS	DEGREE OF GASTRIC ACIDITY	ABSORPTION TIME IN MINUTES		
					ORAL	DUODENAL	RECTAL
71	34	F	Chronic cholelithiasis	Normal	18	16	16
72	47	M	Pyloric ulcer	Hyper.	33	23	23
74	39	M	Duodenal ulcer	Hyper.	33	25	28
75	27	F	Colitis	Hypo.	27	22	26
76	36	M	Ulcerative colitis and chronic procto-sigmoiditis	Normal	37	20	9
77	29	M	Duodenal ulcer	Hyper.	26	19	23
78	56	F	Arteriosclerosis	Normal	21	19	15
79	28	F	Chronic cholecystitis	Normal	33	19	22
80	18	F	Migraine	Normal	24	23	20
81	62	M	Carcinoma of colon (sigmoid)	Hypo.	18	15	16
82	28	F	Chronic cholecystitis	Hypo.	9	13	10
83	31	M	Duodenal ulcer	Hyper.	32	20	23
84	56	M	Chronic gastritis	Hypo.	16	13	16
85	26	F	Gastric neurosis	Normal	14	13	15
				Average	24.3	18.6	18.7

Comparative studies were made on fourteen patients to determine the relative rapidity of absorption following oral, intraduodenal, and rectal administration in each case. The three tests were made on each patient at intervals of several days, every effort being made to achieve uniformity in technique and in experimental conditions. The results of these studies are tabulated in Table II. The rates of absorption from the rectum in this series varied from 9 to 28 minutes. The average rate for this route of administration for the fourteen cases was 18.7 minutes, a figure which was practically identical with the intraduodenal rate of 18.6 for the same series of cases. The oral rate in this study, however, was several minutes slower, averaging 24.3 minutes for the same series.

The relation of gastric acidity to absorption from the rectum was also studied in this selected series of cases (Table III). It was found that the absorption was slowest in cases with gastric hyperacidity. In the latter group, the average was 24.2 minutes, as compared to 16.1 and 17.0 minutes for the normal and hypoacidity groups, respectively, in the same series of cases.

TABLE III

RELATION OF GASTRIC ACIDITY TO ABSORPTION RATES FOLLOWING ORAL, DUODENAL, AND RECTAL ADMINISTRATIONS OF PEANUT PROTEIN IN FOURTEEN CASES

DEGREE OF GASTRIC ACIDITY	NUMBER OF CASES	AVERAGE ABSORPTION TIME IN MINUTES		
		ORAL	DUODENAL	RECTAL
Hypoacidity	4	17.5	15.7	17.0
Normal	6	24.5	18.3	16.1
Hyperacidity	4	31.0	21.7	24.2

The normal acidity group average of 16.1 minutes appeared to be more rapid than the hypoacidity reading (17 minutes) for the first time in any of our studies. This probably was the result of the small number of cases in this group and of the unusual low reading of 9 minutes in Case 76 (nonspecific ulcerative colitis), a patient in whom the presence of active ulceration in the lower bowel accelerated absorption to an unusual degree (Table II).

The effect of bowel ulceration upon rapidity of absorption had also been noted in the previous study with egg.[3] In a case of ulcerative colitis (listed as Case 7 of Table III in that study), an absorption rate of 7 minutes was obtained following rectal administration of the egg antigen. In three other cases without ulcerative lesions, in the same series, the absorption rates were 26, 65, and 125 minutes, respectively. The ulcerative case was again tested at a later date when the ulcerative process was healing. At this time a rectal absorption time of 26 minutes was obtained.

Of interest is the relation of the absorption rate from the rectum to gastric acidity. It had been noted in previous studies[1, 2] that, following oral and duodenal administration of the peanut antigen, the absorption rate was definitely retarded in cases with gastric hyperacidity. The same finding had been noted in the rectal studies with the egg antigen.[3] In the present studies, with the rectal administration of the peanut antigen, the same principle was found to hold true.

In view of these findings, studies were made on about forty subjects to determine whether or not there was any relationship between gastric acidity and rectal pH. The patients studied were all on normal diets. Only the pH of the rectal washings, and not that of the feces, was studied. The rectum was washed with warm tap water, and the pH was immediately determined by means of the Heilige-Klett colorimeter. In ten of the patients, two or more studies of the rectal

pH were done on successive days to determine whether or not there was any daily variation in the readings. The results obtained in each patient did not vary materially from day to day.

The pH readings in this series ranged from 6.4 to 7.4. There were no striking differences in the rectal pH readings of patients with varying degrees of gastric acidity. There was no evidence of an increased acidity in the rectum in cases with gastric hyperacidity, which would account for the slower absorption of antigen in these cases.

DISCUSSION

Sussman, Davidson, and Walzer reported that the absorption of egg protein from the rectum was slower than that following its oral administration. This impression was gained in studies on only a few cases in which no standard technique was employed. In the present study with peanut antigen, carried out under more uniform experimental conditions, this earlier impression could not be confirmed. One may conclude from the comparative studies on fourteen selected cases (Table II) that the average rectal and duodenal absorption rates with the peanut antigen closely approximate each other. Absorption following oral administration of the antigen was slower by about 5.6 minutes than the rectal and duodenal rates.

In attempting to explain this difference several factors must be kept in mind. Mechanical factors, such as peristaltic activity, tonus and spasm of the pylorus, configuration of the stomach, etc., must be considered. The degree of gastric acidity also plays a part. Moreover, the possibility that absorption may take place from the esophagus and stomach must also be taken into account. Absorption from the isolated esophagus and stomach has already been demonstrated experimentally in the *Macacus rhesus* monkey.[6] The relative importance of the above-enumerated factors in influencing the rapidity of absorption of orally administered antigen will form the subject of a future communication.

The fact that the average rectal absorption rate in the series of fourteen selected cases differed little from the duodenal rate is also significant. This finding adds considerable support to the position that the absorbed antigen enters the circulation in an undigested form, for there are no active digestive enzymes in the rectum. Further confirmation is obtained in other studies made with similar techniques in human beings and in monkeys which have demonstrated that the absorption of antigen occurs from the vagina and uterine cervix,[7] from the intact skin,[8] from the peritoneal, pericardial, and pleural cavities, and from the spinal canal.[9]

The technique employed in the above studies is sensitive enough to detect the absorption of as little as 0.0001 mg. of protein nitrogen into

the circulation. The smallness of the amount absorbed does not diminish its importance in the eyes of the allergist, however, for it is sufficient to institute a severe constitutional allergic reaction in the sensitive patient, and in a highly sensitive patient, it is enough to cause death.

CONCLUSIONS

The absorption of unaltered peanut antigen, which was previously shown to occur following oral and intraduodenal administration, is now demonstrated following rectal administration.

The average absorption rate following rectal administration of the peanut antigen approximates that following its intraduodenal introduction and is more rapid than that following its oral ingestion.

In patients with gastric hyperacidity, absorption of peanut antigen from the rectum is slightly retarded, a finding which was also noted following the oral and intraduodenal administration of the antigen in these cases.

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RELATIONSHIPS BETWEEN FOODS AS SHOWN BY THE SKIN TEST IN 1,000 CHILDREN

Some Characteristics of the Skin Test

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IT IS a well-established fact that proteins having similar amino acid compositions and physical-chemical properties exhibit interrelationships in immunologic experiments.[1, 2] These relationships are most commonly evident in proteins from biologically related plants and animals, and have been used by Nuttall and others[3] to study interspecific zoological relationships and to provide independent confirmation of the classifications worked out from morphologic considerations. There are also many instances among proteins in which chemical similarity and coincident antigenic relationship may be attributed to similarity of function, the best known instances being the similarity between crystalline lens proteins and between keratins from diverse animal species.

We have made a study of the question of whether skin tests in allergic individuals show specificities which can be related to botanical and zoological relationships between foods. The problem has been approached from two angles: first, whether skin testing will indicate biologic relationships similar to those indicated by morphology; and second, whether cross reactions are obtained to allergenic food protein preparations which are known to contain immunologically related proteins.

Laboratory immunologic experiments intended to clarify botanical relationships in plants have yielded controversial results.[4] As Landsteiner points out, the conditions encountered are more difficult here than in the study of zoological relationship, where blood serum provides an admirable material with which to work, free from substances which inhibit the reactions or produce nonspecific precipitation with antisera, and containing a high concentration of antigenic proteins.

Food preparations for allergic testing, in addition to being difficult to prepare free of substances having irritating qualities and causing a high incidence of skin reactions in nonsensitive persons,[5] are obtained from parts of the plants whose function is often highly specialized. They are, therefore, unlikely to contain equal quantities of protein materials whose chemical compositions and properties result in specific

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differences. Even in the pollens, which have been studied to some extent from this viewpoint,[6-9] it might be expected to find that, as with fibrinogen in mammals,[10] similarity in function has resulted in similarity of chemical compositions and properties sufficient to obscure evidences of specific relationships in many cases.

A botanical classification of the plants yielding common foodstuffs was presented by Vaughan,[11] and extended by Ellis.[12] It has found its way into several recent textbooks on clinical allergy as a logical basis for carrying out food testing, undoubtedly as a result of uncritical acceptance of the advantages claimed by Vaughan for the usefulness of the classification for this purpose. Vaughan himself did not show that his claims were substantiated by evidence. He stated that the data he presented in support of this thesis did not lend itself well to statistical interpretation. We have examined his data and supplemented it with sufficient additional material to give decisive answers to the questions involved.

The second part of our study, on the skin reactions to food allergens known to contain immunologically related proteins, is interesting from two points of view. It provides evidence that allergic skin reactions parallel other immunologic phenomena in their specificity relationships, and it has led us to an estimate of the reliability of the skin test itself under certain special conditions.

MATERIALS, METHODS, AND TERMINOLOGY

The 10 cases reported by Vaughan were tested to 61 individual food extracts containing 0.08 mg. of total nitrogen per milliliter and to 13 pooled food extracts made up to contain 0.08 mg. of total nitrogen per milliliter from each of the individual foods represented. In our counting of his reported reactions to these extracts, we decided to include borderline reactions as well as the definite positives because, (1) Vaughan considered them significant, (2) their inclusion gave desirably larger numbers for statistical analysis, and (3) the general conclusions which could be drawn would not be appreciably affected by their exclusion.

Our own data were obtained from the results of skin tests of 1,000 children under 13 years of age, completely tested to extracts of allergenic protein preparations of 80 common foods and of 16 epidermal substances. This work was done in our allergy clinic at the Children's Hospital, Los Angeles.

All tests were done intradermally with 1:1,000 solutions made from stock dry concentrates by our usual technique.[13] They were not standardized by any of the nitrogen content methods because there does not appear to be assurance that any such method measures skin reactivity for food extracts. For example, some of our dry concentrates,

such as that from strawberries, contain less than 1 per cent total nitrogen, and our extracts therefrom contain none precipitable by trichloracetic acid, yet give a relatively high incidence of skin reactions which seem to be specifically related to clinical symptomatology.

These data are suitable for the examination of questions regarding the correlation of reactions to various foods, since they were obtained largely without bias in favor of correlation of particular sets of reactions and under conditions of testing making it almost impossible for any such prejudice to influence the recording of the reactions. The food extracts are arranged alphabetically within groups: cereals, fruits, vegetables, nuts, and meats, so that it is very exceptional for botanically related substances to occur at adjacent sites on the tests. The routine of handling the patients whereby the tests on the arms of several persons are read in rapid succession also renders the general influence of such a prejudice even more unlikely.

Tests were done on the external aspect of the upper arm, or, in small children, on the back. Sixteen extracts were injected each time, eight on each arm, in a dose of approximately 0.01 ml. The reactions were read after a twenty-minute interval.

In tabulating the reactions only definite positive reactions (two-plus or more, on a zero to four-plus scale) were counted. In reading the reactions an effort was made to compensate for the varying sensitivity of different skins. Thus small reactions without whealing were counted as definite positives only in persons on whose arms some completely negative reactions appeared.

The analysis of the data was done throughout by counting the number of coincidental reactions, that is, reactions on a single person to both foods of the pair being considered. Naturally, most of these pairs were not put on simultaneously. This was desirable rather than otherwise, because our study concerns the significance of the skin test as it is usually employed.

It is, of course, obvious that coincidences will occur whether the foods are related or not. An individual may be specifically sensitive to both of two completely unrelated substances. However, it is easy to calculate the number of coincidences of this nature to be expected if the number of persons tested and the numbers of all reactions to each of the two substances are known. The expected number of coincidences is the product of the latter two numbers, divided by the former, i.e.,

$$\text{Expected coincidences} = \frac{(\text{Reactions to A})\ (\text{Reactions to B})}{\text{Number persons tested to A and B}}.$$

That this relationship is true is easily evident. When we say the reactions to two foods are unrelated, we mean that whether a person reacts to one or not will not influence his chance of reacting to the other. Thus, if a certain fraction of the persons who react to the first food

also react to the second, the same fraction of the persons who do not react to the first food will be expected to react to the second. This fraction is the number of persons reacting to the second food, divided by the total number tested. This fraction, multiplied by the number of persons reacting to the first food, gives the expected number of coincidences. That this is so may readily be seen by reference to Fig. 1, where the area of the rectangle represents the number of persons tested, and areas marked with A's represent persons reacting to one food, and areas marked with X's represent persons reacting to the second food. The fraction is then:

$$f_1 = \frac{AX + BX}{AX + AY + BX + BY} = \frac{AX}{AX + AY} = \frac{BX}{BX + BY}$$

It is evident that this argument assumes that all the persons tested are equally capable of reacting to the substances used, and that some randomly acting factor or factors determine whether they do or do not. In other words, it assumes that the population is homogeneous. Inhomogeneity causes the found coincidences for unrelated foods to exceed the calculated expected ones, whether it is due to the addition to a homogeneous population of persons lacking in some degree the capacity to react or of persons reacting excessively.

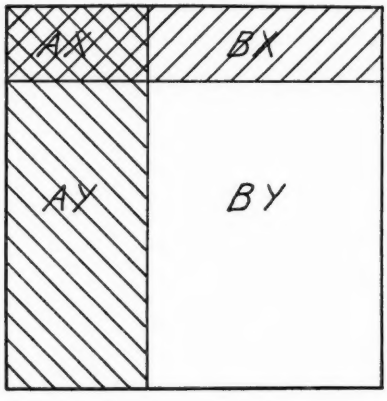

Fig. 1.—Diagram illustrating independence (lack of correlation) between two attributes of a population. The areas represent the number of individuals of the group examined who fall into the four classes when the attributes are independently distributed and the total number is sufficiently large that random fluctuations are negligible: 1, those who have both attributes (area *AX*); 2, those who have only one (area *AY*); 3, those who have only the other (area *BX*); and 4, those who have neither (area *BY*).

Two distinct conclusions can be drawn from these counts and calculations. In case the number of coincidences found exceeds the expected number, we may estimate both the degree and significance of the correlation found between the foods by means of the skin test. An easily interpreted measure of the degree is the quotient, k, of the found number divided by the expected number. Except for accidental

fluctuations, this figure will not be changed by increasing the number of persons included in the count.

The significance of the correlation is estimated only in a negative manner in the absence of some theory capable of predicting the degree of correlation to be expected. The most suitable method is the use of the chi-square test,[14] which tells how certainly the assumptions used as a basis for calculating the expected figures are proved false in a particular instance. This test is suitable for measuring the significance of departures of observed from expected values of a variable, without regard to the nature of the assumptions used to obtain the expected figure. Its theoretical justification is a complex problem in the statistical theory of distributions, and is beyond the scope of this paper.[15, 16]

In order to extract all the relevant information from the data in cases of tests of independence, it is necessary to sum the contributions to chi square from the four observed and four expected figures, which can be simply calculated from the theory outlined above. These are the numbers of persons reacting to each one alone, and of persons reacting to both and to neither. The discussion of terminology contains the condensed expression used for this purpose. The value of chi square, in contrast to the value of k, does not tend to a fixed limit as the size of the population is increased. Thus, with a large population, a small degree of correlation may be demonstrated as conclusively as a high correlation when fewer test subjects are used.

In order for the value of chi square to have any meaning, the smallest found or expected number should be at least 10.

From the value of chi square obtained one may get, by calculation or by reference to tables,[14, 17, 18] a value called P, which represents the probability that the number of coincidences found differed by accident from those expected. Thus, if P = 0.02 there is only one chance in 50 that the two numbers differ to the observed extent as a result of random fluctuation. Values of P this small or smaller are by convention considered to indicate a contradiction of one or more of the assumptions on the basis of which the expected value has been calculated.

The number of reactions to the first member of a pair of foods is called N_1; those to the second member, N_2; and the observed coincidences, N_c. The number of persons tested (the population) is N. N_{ex}, the expected number of coincidences, is equal to $\frac{N_1 \times N_2}{N}$. The value, k, which is used as a measure of the degree of correlation is equal to $\frac{N_c}{N_{ex}}$.

Chi square is calculated by the formula: $\chi^2 = \frac{(N_c N - N_1 N_2)^2 N}{N_1 N_2 (N - N_1)(N - N_2)}$

P is the probability explained above.

When a corrected value of N_{ex} is determined, this figure N_{ex}' and N_c are alone used to calculate chi square, by the relation, $\chi^2 = \frac{(N_c - N_{ex}')^2}{N_{ex}'}$. From this value of chi square a revised value of P, called P′, is obtained. It was believed that this procedure was better justified theoretically than the approximately equivalent one of correcting N_c and using the relation given in the preceding paragraph to calculate chi square. N_{ex}' is also used to calculate a new value of k, called k′.

RESULTS OF TESTING WITH BOTANICALLY RELATED FOODS

Since the greatest number of cross reactions to any pair of foods in Vaughan's data was three, it is obviously inadequate to establish relationship between a chosen pair. However, by counting the total number of crosses within each group of related foods for which a pooled test solution was given, and estimating and totaling the number of crosses which would be expected by accident within the same group, it was possible to obtain an estimate of the significance of the interrelationship within the groups. Using this method of counting, only the number of coincidences and the expected number of coincidences are available for calculation of chi square, and the estimates of P are accordingly somewhat more conservative than they would ordinarily be. However, this is desirable in view of the small numbers involved. This work is summarized in Table I.

TABLE I

INTERFAMILY FOOD RELATIONSHIP
Analysis of Vaughan's 10 Cases

BOTANICAL FAMILY	N_c	N_{ex}	k	P
Liliaceae	2	1.2		
Juglandaceae	0	0.0		
Chenopodiaceae	0	0.0		
Cruciferae	3	2.4		
Rosaceae	0	0.0		
Pomaceae	0	0.2		
Drupaceae	19	7.5	2.5	<0.01
Leguminosae	23	10.2	2.3	<0.01
Rutaceae	0	0.0		
Umbelliferae	3	2.8		
Solonaceae	1	0.6		
Cucurbitaceae	4	0.8	5.0	
Compositae	0	0.2		
Totals	55	25.9	2.1	<0.01
Controls	16	13.3	1.2	0.5

In the table under "Control" are given the results of comparing approximately two-thirds as many unrelated pairs of substances as the total number of related pairs. These unrelated pairs were obtained by taking the first and last substance in each food group and comparing them with all the substances in the group immediately following, using the same arithmetic method to calculate the expected number of crosses.

We see that these data do give some evidence that cross reactions within the groups exceed expectation. The total number of cross reactions is 2.1 times the expected number. The chi-square test applied to the total leads to the conclusion that it would be obtained by accident only about one time in a thousand. However, inspection of the data shows that the whole of this significance comes from interrelations within three groups: *Drupaceae, Leguminosae,* and *Cucurbitaceae.* The remaining ten groups give totals: expected coincidences, 7.4; found, 9. These figures are in almost exactly the same ratio as the unrelated pairs of foods counted, for which the totals were: expected coincidences, 13.3; found, 16.

Accordingly, we conclude that Vaughan's prediction that cross reactions within the groups will exceed expectation is supported by his data, but much less generally than he indicated; in fact, only within 3 of his 13 tabulated food groups.

Vaughan's justification for the use of pooled extracts was that reactions to groups of substances would be obtained when reactions to individual members were negative, and indeed 17 of the 40 group reactions in his data were obtained under these circumstances. However, some doubt as to the reliability of these reactions is cast by the fact that in 15 instances negative reactions to the mixed allergen for a group were obtained when an individual member of the group was positive. This finding is difficult to account for on a theoretical basis, assuming that the tests are reliable, since the group solution contained an amount of each member of the group equal to the amount in the individual test solution. The significance of these skin reactions is cast further in doubt by the fact that, of 64 foods to which clinical trouble was ascribed, only 27, or 42 per cent, showed positive skin reactions. Also, in 8 of 28 instances in which symptoms were attributed to a member of a group whose mixed antigen was administered, even the group antigen did not show a positive reaction.

The assertion made by Vaughan that a positive reaction to one member of a group of foods should be taken as indicating that other members of the group may cause clinical difficulty, even in the absence of a positive skin reaction, appears, therefore, to lack confirmation, especially since no detailed information was given explaining how decision was reached as to what substances were responsible for the symptoms observed. The patient's own opinion regarding what causes his symptoms is unreliable except in those relatively rare cases where a dramatic train of symptoms promptly follows ingestion of some one or few foods.

In order to obtain an independent confirmation of Vaughan's data, we took 30 cases in sequence from our group of 1,000 cases and tabulated them in the same way, except that no pooled solutions were used for testing. Eleven groups of foods were represented. The *Juglandaceae*

and *Rosaceae* groups were represented by only one food each in our tables, and so could not be used to measure correlation. Other foods omitted from our tabulation were: *Lilaceae,* garlic; *Chenopodiaceae,* Swiss chard; *Umbelliferae,* parsley; *Solonaceae,* eggplant; *Cucurbitaceae,* pumpkin and cucumber.

From Table II it may be seen that for only 3 of these 11 groups was a significant degree of cross-reactioning found, exceeding that probable by accident, namely, in the *Cruciferae, Leguminosae,* and *Umbelliferae.* Thus our data agrees with Vaughan's only in respect to the one group, the *Leguminosae.* Control pairs of unrelated foods, selected as before, are also tabulated and show a positive correlation just as they did in Vaughan's data, but to a more marked degree. This phenomenon is discussed in more detail below.

TABLE II

INTERFAMILY FOOD RELATIONSHIP
30 Cases

BOTANICAL FAMILY	N_c	N_{ex}	k	P
Liliaceae	3	3.0	1.0	
Chenopodiaceae	1	1.5	0.7	
Cruciferae	10	4.4	2.3	0.01
Pomaceae	2	0.9	2.2	
Drupaceae	10	7.5	1.3	0.4
Leguminosae	50	26.5	1.9	<0.01
Rutaceae	9	5.4	1.7	0.2
Umbelliferae	14	6.4	2.2	<0.01
Solonaceae	4	2.4	1.7	
Cucurbitaceae	6	5.8	1.0	
Compositae	4	2.7	1.5	
Totals	113	65.5	1.73	<0.01
Controls	95	69.4	1.37	<0.01

With the whole of the data for 1,000 cases it becomes possible to examine selected pairs of foods for relationship. Those we chose for this examination fall into four classes: 1, a group of eight pairs of foods known to contain related proteins, either because of other immunologic experimentation, or because of common origin, such as cow milk casein and cow milk whey; 2, a group of ten pairs for which neither botanical classification nor previous experimentation had shown relationship; 3, a group of ten pairs related by the botanical classification, but in no other known way; and 4, four pairs unrelated as in group 2, but consisting of substances to which clinical trouble is frequently attributed. So far as possible, we selected foods for groups 2 and 3 that were specifically mentioned by Vaughan as unrelated or related.

We counted the total number of skin reactions to each of these foods separately, and the number of coincidences between pairs for the 1,000 patients, 974 of whom showed skin reactions to one or more of the 96 extracts included in the tabulation. We calculated the number of

coincidences to be expected by accident on the assumptions that the population is homogeneous and that coincidence is purely accidental, as outlined above. However, when done in this way, the number of coincidences turns out to exceed the number of expected coincidences by significant amounts for all pairs of substances. Evidently the population is inhomogeneous in this respect. In order to correct for this lack of homogeneity all the coincidence figures for groups 2 and 4 (unrelated substances) were summed, and also all the expected coincidences, and the first sum divided by the second, giving 1.503. Then all the expected coincidence values throughout the table were separately multiplied by this factor to give the corrected expected number of coincidences, and from these figures the values of P′ for the entire thousand cases were calculated.

In addition to the count for the whole group of cases, we attempted to get an idea of the internal consistency of the data by dividing the patients arbitrarily into three groups of about 300 consecutive cases each. These subtotals were treated in the same way except that no allowance was made for the cases reacting to no foods at all (2.6 per cent of the total population), and the correction factor used was correspondingly lower, being 1.467. Table III shows the values of P′ so found. The next to the last column gives our estimate of the significance of the relationships found between the pairs of foods, including the consistency of the three divisions of the general population in the estimate.

It may be seen that of eight pairs of foods known to contain related proteins (group 1) four are found to give significant correlation and two show doubtful cross-reactioning; of ten pairs which would not have been expected to give cross reactions (group 2), two show definite significant relationship by the skin test (it is noteworthy that both of these pairs were mentioned specifically by Vaughan as being unrelated); of ten related botanically (group 3), three show definite and one doubtful relationship—only slightly higher incidence than for the unrelated group; and of four unrelated pairs known to give frequent trouble clinically, two exhibit a questionably significant degree of cross reactioning.

It is possible that the cross reactions of one of the unrelated pairs, white potato-sweet potato, may be due to the presence in both of some similar allergenic substance whose existence is attributable to the similarity of special function of the plant part taken for preparation of the extract. We know of no other explanation to offer for the observed relationship.

It is evident that botanical classification is an unreliable basis for prediction of relationship between individual foods in skin testing, and presumably therefore in the determination of foods responsible for

TABLE III

RELATIONSHIP OF FOOD PAIRS AS INDICATED BY SKIN REACTIONS OF 1,000 CHILDREN

FOOD PAIRS	PROBABILITY (P′) OF NONRELATIONSHIP IN GROUPS OF CASES				INDICATED RELATIONSHIP	CORRELATION DEGREE (k′)
	1ST (307)	2ND (311)	3RD (358)	ALL (1,000)		
Group 1—Immunologically Related						
1. Cow casein —Goat casein	0.1	0.03	0.001	<0.001	Definite	1.51
2. Cow casein —Cow whey	<0.001	<0.001	<0.001	«0.001	Marked	1.76
3. Goat casein —Goat whey	0.002	<0.001	<0.001	«0.001	Marked	1.78
4. Cow whey —Beef	0.2	0.95	0.7	0.5	None	0.89
5. Wheat —Rye	0.02	0.02	0.02	«0.001	Marked	1.54
6. Wheat —Barley	0.01	0.5	0.6	0.03	Doubtful	1.24
7. Rye —Barley	0.3	0.02	0.8	0.05	Doubtful	1.20
8. Pea —Lentil	0.4	0.98	0.5	0.4	None	1.11
Group 2—Unrelated						
9. Beef —Almond	0.5	0.3	0.95	0.7	None	1.04
10. Beef —Apricot	0.7	0.4	0.5	0.2	None	1.14
11. Buckwheat —Wheat	0.02	0.05	0.6	0.005	Definite	1.35
12. White potato —Sweet potato	0.3	0.01	0.003	<0.001	Definite	1.47
13. Spinach —Cabbage	0.1	0.6	0.98	0.5	None	0.93
14. Tomato —Onion	0.4	0.5	0.9	0.4	None	0.94
15. Barley —Orange	0.3	0.08*	0.2	0.03*	None	0.82
16. Carrot —Apricot	0.4	0.8	0.8	0.7	None	0.96
17. Tomato —Brussels sprouts	0.5	0.7	0.6	0.7	None	0.96
18. Barley —Sweet potato	0.4	0.6	0.2	0.07	None	0.79
Group 3—Botanically Related						
19. Almond —Apricot	0.4	0.4	0.3	0.7	None	0.95
20. Peanut —Lima bean	0.7	0.6	0.95	0.6	None	0.95
21. White potato —Tomato	0.8	0.4	0.04	0.05	Doubtful	1.18
22. Beet —Spinach	1.0	0.5	0.4	0.4	None	1.13
23. Turnip —Cabbage	0.2	0.7	0.4	0.9	None	1.01
24. Asparagus —Onion	0.4	0.2	0.8	0.2	None	0.89
25. Orange —Lemon	0.2	0.2	0.01	0.001	Definite	1.27
26. Oat —Rice	0.03	0.1	0.1	0.001	Definite	1.33
27. Buckwheat —Rhubarb	0.7	0.6	0.6	0.98	None	0.99
28. Cauliflower —Broccoli	0.03	0.4	0.02	0.002	Definite	1.37
Group 4—Unrelated						
29. Egg white —Celery	0.4	0.7	0.4	0.2	None	0.85
30. Wheat —Cow whey	0.2	0.03	0.7	0.03	Doubtful	1.28
31. Wheat —Cow casein	0.3	0.08	0.6	0.06	Doubtful	1.24
32. Orange —Cocoa	0.6	0.4	0.9	0.4	None	0.92

*The correlation is negative, and undoubtedly accidental.
< is read "less than," and «, "much less than."

symptoms in allergy.[19, 20] Even known immunologic relationship is not sufficiently dependable to be relied on, a fact that might have been predicted from the known multiplicity of antigenic substances, which must be present in practically all preparations used for allergic diagnosis. It does not necessarily follow that the ability to demonstrate immunologic relationship between a readily isolated protein from one food and another from a second food will mean that these foods will be found to be related by skin test. Too many unknown factors, both

quantitative and qualitative, intervene. Only skin testing with isolated and purified proteins could be expected to yield such a result, and even in this case there would remain the question of the reliability of the skin test itelf as a limitation on the degree of correlation to be expected.

CHARACTERISTICS OF SKIN TEST SHOWN BY TESTS WITH RELATED AND UNRELATED FOODS

All of the unrelated pairs of substances compared show cross-reactioning in excess (by about 1.5 times) of what would be expected on the assumptions of a homogeneous population and of random distribution of the reactions. This has been explained as the result of a lack of uniformity of the population. The alternative explanation, that some nonspecific skin irritative substance or substances is present in all the antigens, is rendered unlikely by the uniformity of the degree of excess cross reactions with food substances that are extremely diverse chemically. It was natural, therefore, for us to attempt to separate the population in accordance with the total number of reactions which each individual showed to the 96 food and epidermal extracts included in the tabulation. We arbitrarily divided the population into persons reacting to more than 35 extracts and those reacting to 35 and less. This divided population was examined for cross reactions between a related pair of foods, cow casein and goat casein, throughout the entire 1,000 cases; and, for the first 307 cases, between ten unrelated pairs, cow casein and each of ten vegetables (broccoli, Brussels sprouts, cabbage, carrot, cauliflower, celery, lentil, lettuce, onion and parsnip).

TABLE IV

SIGNIFICANCE OF REACTIONS IN INDIVIDUALS REACTING TO MANY AND TO FEW SUBSTANCES

UNDIVIDED POPULATION	NO. OF CASES	N_1	N_2	N_c	N_{ex}	N_{ex}'	k	k′	P′ OR P
Related pair (a)	1,000	214	190	92	40.7	61.1	2.26	1.51	<0.001
Unrelated pair (b)	307	74	77	25.5	18.6	27.3	1.37	0.94	0.7
Persons Reacting to More Than 35 of 96 Extracts									
Related pair	204	86	70	43	29.5		1.46		0.01
Unrelated pair	78	36	38.8	17.9	17.9		1.00		1.0
Persons Reacting to Less Than 36 of 96 Extracts									
Related pair	796	128	120	49	19.3	23.2	2.54	2.11	«0.001
Unrelated pair	229	38	38.2	7.6	6.3	(c)	1.2		0.6

(a) Related pair used was cow casein and goat casein.
(b) Unrelated pair used was cow casein and a vegetable (averaged from 10 vegetables).
(c) N_{ex}' represents a corrected N_{ex} and equals 1.20 N_{ex} (k is 1.20 for unrelated pair in persons reacting to less than 36 test extracts).

The ten vegetables were alike in their behavior, and their counts were averaged to give a single representative set of figures. The results are shown in Table IV. They allow two very interesting conclusions to be drawn.

First, contrasting the behavior of the unrelated pair of substances for the whole and for the divided populations, it is evident that the division has reduced the degree of cross-reactioning in both parts of the population. In the persons reacting to a large number of the test substances, division has reduced the degree to the point where the prediction made on assumptions of homogeneous population and random distribution of reactions is exactly fulfilled.

Second, the majority of the specific cross reactions, confirming a relationship between the related pair of substances, is found in the population group reacting to less than 36 of the 96 extracts. The difference is small, but it suggests that reactions in persons who respond to relatively few extracts have more significance in diagnosis than those in persons who show many reactions.

It occurred to us that it might be interesting to determine whether it would be possible to increase the specificity of the cross reactions to cow and goat caseins in the whole population by eliminating from consideration all persons reacting to either whey preparation. The count showed that 97 persons reacting to cow casein and 89 persons reacting to goat casein remained, and that the number of coincidences was reduced from 92 to 16. In calculating the values of k and P from these figures some assumption must be made regarding the extent to which the total population is reduced by eliminating persons reacting to whey. The simplest, and the one which will give the smallest value of expected coincidences, and so make the coincidences found appear to have a maximal degree of significance, is that only persons reactive to one or the other, or both, of the wheys should be removed from the population. These persons total 301, so the population becomes 699. This leads to values of k and P of 1.29 and 0.2, respectively. In other words, no indication of significant relationship is observable under these circumstances.

This unexpected finding may be explained on any of several bases: the whey preparations contain sufficient casein to provoke a reaction in most persons specifically sensitive to casein; or one or both of the casein preparations yield so little casein on extraction with buffered saline at pH 7.0 as not to produce casein-specific reactions, the reactioning observed being due to the unavoidable slight contamination with whey proteins and to nonspecific irritation or trauma.

A preliminary approach to a more fundamental question may be made through examination of our data; that is, how reliable is the skin test as an indicator of genuine cutaneous sensitivity to substances in our test extracts? Taking the pair of substances on our list showing the highest correlation, namely, goat's milk casein and goat whey, we can calculate the minimum fraction of the reactions which must be specific in order to produce this degree of cross-reactioning.

By subtracting the figure 79, obtained by trial, from the total population of 1,000, from the 194 and 195 reactions to the goat casein and whey, respectively, and from the 101 coincidences found, we obtain a set of figures for which the expected number of coincidences, corrected as before by multiplying by 1.503, is equal to the 22 coincidences remaining. At least $\frac{2 \times 79}{194 + 195}$, or 41 per cent, of these reactions must be specific.

The limitations of this analysis are obvious: the foods tested were not the same, and no estimate of the number of specific reactions to substances not common to the two antigens can be made. We are approaching this same question more directly by making an extensive series of tests with a single test solution. The information which this procedure yields will be reported shortly.

SUMMARY

1. A statistical analysis of the value of a botanical classification of foods in predicting skin reactivity or clinical sensitivity to a food when reactivity to a botanically related food is known, shows it to be unreliable.

2. Foods which are known to contain identical proteins, or proteins which can be shown by immunologic experiments in the laboratory to be related, tend to give a high degree of cross-reactioning by skin test. Exceptions occur, as would be expected from the facts regarding the composition and methods of preparation of the test solutions. The results as a whole support the theory that allergic reactions parallel other reactions of immunity in their specificity relations.

3. Evidence is given that skin reactions are a less reliable guide to specific sensitivity in persons reacting to many substances than in persons giving relatively few reactions.

4. An analysis of the reactions to foods known to be related shows that under some circumstances at least 41 per cent of reactions to a food are specific. It should be emphasized that this is an estimate only of the minimum accuracy under particular circumstances, and that the over-all reliability of food skin tests may be either lower or higher. It also applies only when a single test is made with each food. Naturally, confirmatory testing greatly increases the dependability of the results.

5. The necessity for the use of statistical methods to obtain definite answers to questions such as these is again emphasized.

We are indebted to Dr. Gordon A. Alles for advice and criticism throughout the work and for helpful suggestions in the preparation of the manuscript.

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DISCUSSION

DR. HERBERT J. RINKEL, Kansas City, Mo.—I do not have statistics available that indicate whether or not skin reactions correspond to the genetic relationship of foods. However, from the standpoint of clinical sensitization, I have always been of the opinion that the incidence of food in the diet has more to do with the presence of clinical allergy than the botanical relationship.

I should like to ask Dr. Piness whether he feels the frequency of the food in the diet would in any way affect the problem he is working upon. I realize that in dealing with a large number of patients he has obviated part of that possibility, but I should like to have his discussion as to the importance of the diet, that is, the frequency of the use of the various foods over a period of time.

Without going into statistics, I can agree with him that we do find cross reactions in the *leguminosae* and the *liliaceae* family more than in any other groups.

The other problem I should like to have Dr. Piness discuss is whether or not he feels that the variation in the skin reaction from time to time influences the accuracy of the statistics.

DR. WARREN T. VAUGHAN, Richmond.—With apologies to Dr. Piness, I did not think the meeting was going to start as early as it did this afternoon, and I came in only after Dr. Alexander had rung the bell;

therefore, I am not in a position to discuss his paper, only his conclusions.

I will not attempt to review the observations of Withers and Baldwin, because I presume he has done so. The only point that I should like to make in discussing what I heard is that the suggestion of the use of biologic food groups in the study of allergy was based upon the fact that skin tests were not worth very much in testing with foods; that there were too many false positives, too many false negatives, and that there was too little correlation that could be obtained; that the anamnestic survey and the experiences of the patient afterward were of much importance; and that when one paid attention particularly to the latter, one found frequent correlation between sensitization within biologic groups. In my original paper there were certain curious exceptions, particularly in the potato-tomato group, where, although one would feel that there should be frequent cross-reactions, there were very few. Withers found the same thing.

DR. I. S. KAHN, San Antonio.—I should like to ask a question. In a number of our clinical and skin-test positive milk cases, we have been securing definite positive skin tests to beef extracts in patients in whom we have been unable to determine any clinical sensitivity to beef. I wonder if Dr. Piness has had any similar experience?

DR. PINESS.—The question was asked by Dr. Rinkel as to frequency of foods in a diet being a factor in producing reactions. I believe that concentration of certain foods in the diet may be a factor. The variability of the skin reactions themselves is, after all, a personal equation. I think that when we see the reports of what different skin reactions are and how they are interpreted, we should not consider that as a great part of the general picture.

In studying the skin reactions in this group of cases, we tried to make it as unbiased as possible by having 3 individuals read the reactions without knowing what the others had read and then comparing them, but we found that we came very close in all respects except on 2, which we included because Vaughan claimed that the borderline cases were rather important.

Dr. Vaughan, I think, is a little mistaken in stating that I mentioned that these skin tests were unreliable. I made no such mention. I merely said that, when there were a large number of tests done in such large numbers, often those who reacted to a great many things were not as reliable as those who reacted to a few things.

As far as Dr. Kahn's question is concerned, I don't know, frankly.

THE FALLIBILITY OF THE AUTOPASSIVE TRANSFER TEST (COWIE)

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IN THE last ten years considerable progress has been made in the technique and interpretation of the cutaneous tests employed in the study of allergic subjects. Moreover, the method of preparation as well as the potency of the test substances have also been improved. Yet, far too many patients who are clinically sensitive to material substances, especially to foods, fail to show positive reactions to the cutaneous tests (scratch and intradermal techniques). Any new method or modification of existing methods of testing which will lower the incidence of negative cutaneous reactions to allergens in patients who are clinically sensitive will prove to be of great assistance to a clearer understanding and quicker solution of the causal factors of the allergic syndrome under investigation.

Cowie[1] reported that the skin of an allergic person which failed to react to the intradermal injection of allergens to which he is clinically sensitive may be made to react by the passive transfer of his own blood serum into his own skin. This phenomenon Cowie designated "autopassive transfer." Cowie also claimed that positive intradermal reactions are very often enhanced by autopassive transfer. His basis for performing this test was on the hypothesis that it was a simple matter to inject the patient's skin with his own antibody-laden blood serum, and so a reaction should occur when specific antigen is injected into the treated area because of the added concentrated antibody. Moreover, Cowie maintained that autopassive transfer may be used as a practical method of examination when passive transfer is indicated, but it cannot replace the Prausnitz-Küstner method. Autopassive transfer is an interesting phenomenon, and its sponsor believes it opens up a new approach to the study of the fundamental principles of skin allergy if independent observations confirm those he reported.

In an effort to corroborate Cowie's work, 15 patients (8 men and 7 women), ranging in age from 18 to 45 years, were selected for study.

MATERIALS AND METHODS

Fifteen cubic centimeters of blood were obtained under aseptic conditions. The blood was permitted to clot, then centrifuged, and the serum drawn off and passed through a Seitz filter. One-tenth cubic

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centimeter of serum was injected into each skin site, and one to two days later it was intradermally tested with approximately 0.02 c.c. of the allergenic extract. Not more than six skin sites were prepared in the outer aspect of each arm on three separate sittings. Each site was tested only once. The control tests were placed 5 cm. laterally from the sensitized areas which were not closer than 3.5 cm. The number of autopassive transfer (indirect method) and control (direct method) tests was 524 for each method of testing. When the food allergens were employed, the patients were requested not to ingest the foods or those in the same biologic group for at least forty-eight hours prior to the preparation of the sensitized areas.

All the patients were routinely tested by the scratch method with the dry powdered extracts for sensitivity to food, pollens, and inhalant substances. Dry, powdered, natural pollen was used. The pollens of short and giant ragweed, timothy, red top, orchard and June grasses, and oak, were employed for testing. When reactions to the scratch tests were negative, the intradermal tests with the 1:50 dilution of extracts were next performed. Plus-minus reactions, although recorded in Table I, were interpreted as negative, because I have found repeatedly that patients with such reactions (especially with the 1:50 dilution of pollen) showed no correlation between the reactions and the clinical symptoms. All the extracts employed for the intradermal tests were prepared after the method of Coca. House dust, quince, karaya gum, and tragacanth extracts were used in maximum concentration. The remaining extracts were in concentrations as commonly employed for routine testing and were as follows: wheat, corn, rice, oat, barley, egg white, milk, tomato, white potato, green pea, string bean, beef, chicken meat, lamb, rye, spinach, celery, carrot, orange, banana, and chocolate; mixed feathers, horse serum, orris and pyrethrum; sheep, cat, dog, goat, and horse epithelium. I have recorded the intradermal reactions according to the method of Cooke.[2] The details of the technique of the tests and the types of reactions were described by Peshkin and Fineman.[3] All reactions ranging from negative to three plus, which were obtained by the direct and autopassive transfer (indirect) method of testing, are recorded in Table I.

As previously stated the autopassive transfer and control tests were performed only when the scratch tests to corresponding allergens were negative, because it was felt that this was the best means of determining the efficaciousness of the so-called autopassive transfer test.

COMPARATIVE INTRACUTANEOUS REACTIONS TO ALLERGENS

Table I shows the number of intradermal reactions with the direct method ranging from negative to three plus to foods, inhalants, and pollens, and the corresponding reactions obtained with the autopassive transfer (indirect) method.

TABLE I

CORRESPONDING INTRADERMAL REACTIONS WITH THE DIRECT AND INDIRECT (AUTO-PASSIVE TRANSFER) METHODS OF SKIN TESTING TO FOOD, INHALANTS, AND POLLEN IN 15 ADULTS WITH ALLERGY

FOOD ALLERGENS							
	DIRECT METHOD	INDIRECT METHOD					
		NUMBER OF REACTIONS					
CUTANEOUS REACTIONS	NUMBER	NEGATIVE		POSITIVE			TOTAL POSITIVE
		−	±	+	++	+++	
1 plus	23	4	5	13	1	0	14
2 plus	10	0	0	5	4	1	10
3 plus	6	0	0	0	2	4	6
Total positive	39	4	5	18	7	5	30
Plus-minus	4	3	1	0	0	0	0
Negative	272	271	1	0	0	0	0
Total negative	276	274	2	0	0	0	0
Total	315	278	7	18	7	5	30
Inhalant Allergens							
1 plus	15	1	5	9	0	0	9
2 plus	11	0	1	6	4	0	10
3 plus	6	0	0	0	2	4	6
Total positive	32	1	6	15	6	4	25
Plus-minus	4	0	1	3	0	0	3
Negative	99	99	0	0	0	0	0
Total negative	103	99	1	3	0	0	3
Total	135	100	7	18	6	4	28
Pollens							
1 plus	2	0	0	2	0	0	2
2 plus	1	0	0	1	0	0	1
Total positive	3	0	0	3	0	0	3
Plus-minus	3	3	0	0	0	0	0
Total negative	70	70	0	0	0	0	0
Total	73	70	0	3	0	0	3
Summary							
1 plus	40	5	10	24	1	0	25
2 plus	22	0	1	12	8	1	21
3 plus	12	0	0	0	4	8	12
Total positive	74	5	11	36	13	9	58
Plus-minus	11	6	2	3	0	0	3
Negative	439	438	1	0	0	0	0
Total negative	450	444	3	3	0	0	3
Grand total	524	449	14	39	13	9	61

The table shows that of the patients tested to food allergens there were 39 reactions positive with the direct test and only 30, or 77 per cent, reactions positive with the indirect test. All the negative reactions with the direct test were also negative with the indirect method.

Of the patients tested to inhalant allergens there were 32 reactions positive with the direct test and only 25, or 78 per cent, reactions positive with the indirect test. There were 99 completely negative reactions with the direct and indirect methods. Of the 4 plus-minus reactions with the direct test 3 became one-plus reactions with the indirect test. With the intradermal method the difference between one-plus and plus-minus reactions is frequently negligible and so not much significance can be attached to this change.

Of the patients tested to pollens 3 gave positive reactions with the direct test and all gave positive reactions with the indirect test. All 70 negative reactions with the direct test were also negative with the indirect method.

In summary, of a total of 524 tests there were 74 positive reactions to food, inhalant, and pollen allergens with the direct test, and 58, or 78 per cent, reactions positive with the indirect tests. Of the remaining 450 tests 439 were negative with the direct and indirect methods, and 11 were plus-minus reactions with the direct test; and 6 negative, 2 plus-minus, and 3 one-plus reactions with the indirect test. Thus, of the total number of 450 negative reactions (negative and plus-minus) with the direct test, the corresponding reactions with the autopassive transfer method of testing were negative in 99 per cent.

In this group of patients certain foods were definitely responsible for various allergic symptoms, although the respective cutaneous and intradermal tests (direct and autopassive transfer methods) reacted negatively. In one instance chicken caused wheezing and in another urticaria. Lamb was responsible in one case for wheezing and in another for diarrhea. Egg induced angioneurotic edema, and the ingestion of pork, apple, tomato, and beans resulted in sneezing. Ragweed and grass pollens were the etiologic factors in still another case with pollen asthma. The fact that in none of these patients were positive reactions obtained is indeed significant.

All these findings fail to confirm the observations reported by Cowie that an allergic person's skin which fails to react to specific allergen can be passively sensitized with his own serum; and they further fail to suggest that the inactive skin is made to react by bringing more specific antibody to it. Furthermore, it is of interest to note that the skin of an allergic person that reacts to the injection of specific allergen is not made to react more vigorously by the introduction of "more and concentrated specific antibody into it." As a matter of fact, the method of autopassive transfer appears to definitely inhibit an appreciable percentage of reactions which with the direct method of testing were positive. This finding is contrary to those reported by Cowie.

In the final analysis it seems reasonably clear that the failure of the skin of an allergic person to react to a specific allergen to which he is clinically sensitive involves a mechanism that is more complex and probably independent of that which controls reagin antibody.

SUMMARY

1. The skin of an allergic person which fails to react to specific allergen cannot be passively sensitized with his own serum (autopassive transfer).

2. The skin of an allergic person which reacts to specific allergen by direct test shows a 22 per cent drop in positive reactions with auto-passive transfer, indicating some inhibitory rather than enhanced influence.

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CHRONIC HYPERPLASTIC SINUSITIS IN ALLERGIC PATIENTS

A Bacteriologic Study of Two Hundred Operative Cases

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THERE still seems to exist among allergists and bacteriologists a difference of opinion as to whether the hyperplastic form of sinusitis is due to a sensitization to air-borne substances and to foods that can be determined by a positive skin test or whether it is due primarily and solely to an infection. In a previous paper from this clinic, Grove and Cooke[1] expressed the opinion that hyperplastic sinusitis was caused solely by infection, which produced a special pathologic response conditioned by the allergic constitution of the patient.

In further support of this point of view, we now present a study of the bacteriology of 200 operative cases, with a report of a preoperative bacteriologic examination of the washings or surface swabs and a thorough study, bacteriologic and pathologic, of the sinus membranes removed at operation.

Many studies of the bacteriology of sinusitis based on the cultures of swabs and washings are found in the literature, but only a few investigators have given detailed reports of cultures of sinus membranes. Apparently no such studies have been made of a large number of cases of hyperplastic sinusitis limited to allergic patients. Among the papers dealing with the bacteriology of suppurative sinusitis, there are those of Lewis and Turner,[2, 3] Babcock,[4] Dean and Armstrong,[5] Crowe and Thatcher-Neville,[6] Watson-Williams,[7] Wirth,[8] Ashley and Frick,[9] and Balmer.[10] Kistner,[11] in a comprehensive study of the histology and bacteriology of sinusitis, reported on the cultures of membranes removed from 400 patients with nonpurulent sinusitis. This group included some allergic cases, but the number was not given. Kistner stated: "Although hyperplastic sinuses are not suppurating, they are usually infected with pathogenic organisms, the streptococcus predominating. A mixture of bacteria was usually found in each case. A pure culture of one organism was seldom found in cases of chronic sinusitis. In these tissues the streptococci were the most constant, being present in 94.5 per cent of the sinuses; 35 per cent of these were hemolytic beta, 33 per cent hemolytic green-producing or alpha, 14 per cent *Streptococcus viridans*, and 18 per cent nonhemolytic streptococcus of gamma type. In addition to, and in combination with, the streptococci, we found in the order of their

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frequency: staphylococcus, *Micrococcus catarrhalis,* pneumococcus, Friedländer's bacillus, influenza bacillus, colon bacillus, diphtheroids, and streptothrix."

The membranes from the sinuses used in our study were obtained from 200 patients, all of whom had some allergic manifestation. Patients with asthma made up four-fifths of the group. One of these patients had lupus erythematosus and another had periarteritis nodosa. The classification of the entire group is detailed in Table I.

TABLE I

ALLERGY	NO. OF CASES	NO. OF CASES WITH ASSOCIATED ALLERGIES
Asthma	165	25
Hay fever	25	11
Vasomotor rhinitis	12	5
Urticaria and angioneurotic edema	7	4
Eczema	33	2
Vernal catarrh	1	1
Migraine	1	1

One hundred of the 200 patients showed one or more positive skin tests of a moderate or marked degree. But these sensitizations were not all regarded as clinically significant by the allergist, and in many cases when a test or the history indicated clinical sensitization, it did not adequately explain the existing allergy. For example, the elimination of danders and foods in a great many patients who showed skin reactions did not effect any improvement in their asthma. Also, 108 patients were specially questioned regarding aspirin reactions. Twenty-nine of them gave conclusive histories of acute asthmatic or urticarial reactions following its use; but, without the drug, chronic symptoms continued and required another etiologic diagnosis.

A few of the ethmoidal and sphenoidal specimens were procured by simple polypectomy, but the majority represent exenteration of these sinuses. The maxillary membranes were obtained by a Caldwell-Luc operation. All of these operations were performed during a quiescent state; hence, these cultural findings do not represent the bacterial flora of acute sinusitis. The tissues removed at operation were placed in sterile glycerin and sent immediately to the laboratory where, in a special sterile room, they were washed in 95 per cent alcohol, flamed and ground in a sterile mortar, and the material cultured on poured blood-agar plates and in beef infusion broth. Cultures were examined at the end of 12, 24, 48 and 72 hours. Some of the tissue specimens were also examined microscopically for bacteria, the methylthionine chloride (U.S.P.) (methylene blue) and Gram stains being used. The washings from antra were obtained by puncturing the inferior meatal wall with a Coakley trocar or a 19-gauge spinal puncture needle, either flushing the antrum with sterile 0.85 per cent salt solution and withdrawing a small amount for culture, or collecting the return flow. Swab cultures were made from

the ethmoids, and washings were collected from the sphenoids. Approximately 40 per cent of the cultured washings were obtained only once from an individual patient, but in many others there were from five to eight cultures over a period of time. Such washing and swab cultures were occasionally made during an exacerbation, but the majority of these were also secured during a chronic quiescent period.

Three hundred and sixty-five cultures were made of washings from the sinuses, over 90 per cent being antral. One hundred and thirty cultures were made of the membranes removed from ethmoidal and sphenoidal sinuses, and 108 cultures were made of antral membranes.

Table II gives in detail the bacteriologic findings obtained from cultures of the sinus washings and membranes.

Staphylococcus of some form is by far the most frequent organism found in the sinus washings as well as in the sinus membranes (Table II). Hemolytic streptococci were found more frequently in the antral

TABLE II

THE BACTERIOLOGIC FINDINGS IN 200 OPERATIVE CASES OF CHRONIC HYPERPLASTIC SINUSITIS OCCURRING IN ALLERGIC PATIENTS

ORGANISM	SINUS WASHINGS (365 CASES)		ANTRUM MEMBRANES (108 CASES)		ETHMOID AND SPHENOID MEMBRANES (130 CASES)	
	NO.	%	NO.	%	NO.	%
Staphylococcus	224	60	62	57	96	74
Staphylococcus albus	67		16		11	
Staphylococcus aureus	102		20		23	
Hemolytic *Staphylococcus albus*	22		11		39	
Hemolytic *Staphylococcus aureus*	33		15		23	
Streptococcus	84	22.1	78	32	27	20.8
Hemolytic streptococcus	43	11.7	27	25	11	8.5
Indifferent streptococcus	12		4		2	
Streptococcus viridans	29		47		14	
Pneumococcus	52	14	42	3.9	12	9
Micrococcus catarrhalis	20		4		0	
Bacillus coli	19		1		4	
Bacillus influenzae	7		0		0	
Bacillus mucosus capsulatus	1		3		1	
Bacillus proteus	6		1		4	
Bacillus subtilis	8		0		0	
Diphtheroid bacillus	10		1		1	
Streptothrix	0		1		0	
Unidentified organisms	21		0		0	
No growth	44	12	5	4	26	20

membranes (25 per cent) than in the sinus washings (11.7 per cent) or in the ethmoidal and sphenoidal membranes (8.5 per cent). Pneumococcus and *Streptococcus viridans* were present much more frequently in the washings and in ethmoidal and sphenoidal membranes than in the antral membranes. The high percentage of the hemolytic streptococcus in the antral membranes indicates its importance as an agent of infection which often may be overlooked. This is well illustrated in one patient who had eight cultures of the antral washings over a period of five years

and showed only pneumococcus and *Streptococcus viridans,* with an occasional staphylococcus. A culture of the left antrum membrane after operation yielded a pure growth of hemolytic streptococcus. In some instances, the hemolytic streptococci and pneumococci have been typed, but we shall discuss these findings in a later paper.

A clear return flow from the antral irrigations may be sterile, but a heavy growth of one or more organisms may be cultured from membranes removed at operation. On the other hand, 64 cases with a positive culture of the washings showed only two membranes with no growth, although special stains showed the presence of bacteria in the tissue. In the total group of cultures of 108 antral membranes, 47 showed a growth of an organism which had not been recovered in the cultures of the previous washings. This does not mean, however, that certain organisms found in the washings were not present also in some of the antral membranes. The cultures of the membranes of the two antra occasionally showed different organisms and quite often were different from those grown from the ethmoidal membranes. Twenty per cent of the ethmoidal and sphenoidal membrane cultures and 12 per cent of the sinus washing cultures were negative. Cultures of the ethmoidal and sphenoidal membranes showed staphylococci more frequently than the cultures of the washings by 14 per cent.

Staphylococci were present in pure culture in 150 (43 per cent) of the 365 washing cultures, in 59 (45 per cent) of the 130 ethmoidal and sphenoidal membranes, and in 19 (18 per cent) of the 108 antral membranes. Hemolytic streptococci, on the other hand, were present in pure culture in 23 (6 per cent) of the 365 washings and in 24 (10 per cent) of the 238 sinus membranes. Pure cultures of all types of organisms were present in 223 (71 per cent) of the 321 positive sinus washings, which is considerably lower than Ashley and Frick's[9] 87 per cent. Thirty-two (30 per cent) of the 108 antral membranes showed a pure culture. More than one organism was cultured from 98 (27 per cent) of the 365 washings and from 71 (70 per cent) of the 108 antral membranes.

The fact that only 4 per cent of the antral membranes showed no growth indicates the importance of sinus membranes as a focus of infection. That 20 per cent of the ethmoidal and sphenoidal membranes showed no growth may be explained by the fact that, earlier in our work, mucous polyps were opened and cultured from within, whereas now we culture the polyp sac and the underlying membranes which are the source of the infection.

Table III shows the percentage of the bacteria more frequently found in sinus washings by us and by two other investigators.

Ninety-five per cent of the antral membranes and 80 per cent of the ethmoidal and sphenoidal membranes showed bacteriologic evidence of

infection, that is, an average of 87 per cent for the total group. Streptococci of all types cultured from the 238 sinus membranes were found in 44 per cent. This is far below the 94.5 per cent Kistner[11] reported for his group of 400 sinus membrane cultures. It is possible that the membranes found in nonpurulent sinusitis, as he describes it, may be more frequently infected with streptococci than the hyperplastic membranes which we find in allergic cases. However, our figures for the occurrence of streptococci in the sinus washings compare favorably with those of

TABLE III

INVESTIGATOR	STAPHYLOCOCCUS (%)	STREPTOCOCCUS (%)	PNEUMOCOCCUS (%)
Ashley and Frick[9]	40.7	23.3	2.4
Crowe and Thatcher-Neville[6]	24.0	60.0	17.0
Grove and Farrior	60.0	22.1	14.0

many other investigators. Previously we[1] have stated clinical observations as well as bacteriologic studies that led us to the conclusion that chronic hyperplastic sinusitis is caused by bacterial infection and represents a special type of bacterial allergy. Our continuing studies, together with bacteriologic findings on later cases here presented, give us no reason for changing this point of view.

SUMMARY

This study consisted of the bacteriologic examination of: (1) 365 washings obtained from the maxillary and sphenoidal sinuses, (2) 130 polyps and membranes removed from the ethmoidal and sphenoidal sinuses, and (3) 108 membranes removed from the maxillary sinuses.

One hundred and sixty-five of our patients had asthma, 25 had hay fever, 12 vasomotor rhinitis, and 7 urticaria and angioneurotic edema. There were two or more manifestations of allergy in one-fourth of the patients.

In order to obtain these membranes, 48 unilateral and 87 bilateral ethmoidectomies and sphenoidectomies, and 47 unilateral and 53 bilateral Caldwell-Luc operations were performed.

The technique of securing the washings and the cultural methods are described. Eighty-eight per cent of all washings, 80 per cent of the ethmoidal and sphenoidal membranes, and 96 per cent of the antral membranes showed bacterial growth.

The frequency with which the organisms were obtained from the cultures is given. The staphylococci predominate in cultures of both washings and membranes. The hemolytic streptococci are found twice as often in the antral membranes as they are in the washings or in the ethmoidal and sphenoidal membranes.

The importance of these bacteriologic findings in 200 cases of hyperplastic sinusitis is discussed.

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PERIARTERITIS NODOSA AND ASTHMA

Case Report

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THE etiology of periarteritis nodosa is unknown and its intra-vitam diagnosis difficult. Recently Cohen, Kline, and Young[1] expressed the opinion that the disease is a manifestation of irreversible allergy occurring in patients suffering from asthma or other allergic states. We think this conception an important one and are recording the history of this patient (1) because it will add another case of periarteritis nodosa occurring in an asthmatic individual and (2) because the diagnosis of periarteritis nodosa was considered seriously during life although biopsy unfortunately failed to establish it with certainty.

CASE REPORT

T. S., a white housewife, 53 years of age, was admitted to the service of the senior author on May 19, 1936, because of increasing pain of four weeks' duration in both legs. The leg pains were preceded by a short infection, supposedly upper respiratory in nature. Both ankles, especially the left, became moderately swollen. The pains were so severe that on several occasions morphine was required for relief. She had no appetite at all, had considerable weight loss, cough, and expectoration. She had had asthma of many years' duration. One son also suffered from asthma.

On examination a restless, emaciated, and dehydrated woman was observed. The lungs were emphysematous. Both apices were dull to percussion, and an occasional râle was audible over the right apex anteriorly. The heart was not enlarged, and no murmurs were audible. The rate at the apex was 120 per minute, and the blood pressure was 130/80. The peripheral arteries were sclerosed; both ankles showed slight edema. The musculature of both legs showed atrophy, but no nerve tenderness was elicited. The patellar reflexes were normal. The dorsalis pedis and posterior tibial vessels were patent.

During the patient's stay of five weeks the temperature fluctuated between 100° and 101° F., and the pulse hovered around 115. She continued to lose weight despite forced nourishment with a high caloric and high vitamin diet. The leg pains remained severe and required opiates for relief. The patellar reflexes gradually diminished until they totally disappeared, and bilateral foot drop also developed.

Examination of the fundus revealed sclerotic vessels but no hemorrhage or exudate. An electrocardiogram showed no abnormalities. A suppurative ethmoiditis was revealed by rhinologic study. Roentgenologic examination of the chest showed bilateral pulmonary tuberculosis with slight cavitation in the right upper lobe and bronchiectasis in both lower lobes. A complete roentgenologic examination of the gastrointestinal tract and the spine showed no abnormalities. Pyelographic study was likewise normal. Several blood counts were performed: the hemoglobin (Sahli) ranged from 76 to 84 per cent; red blood cells, from 3,800,00 to 4,300,000; the leucocyte

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Fig. 1.—Section of artery from fatty tissue in region of nerve. Note perivascular infiltration. (×80.)

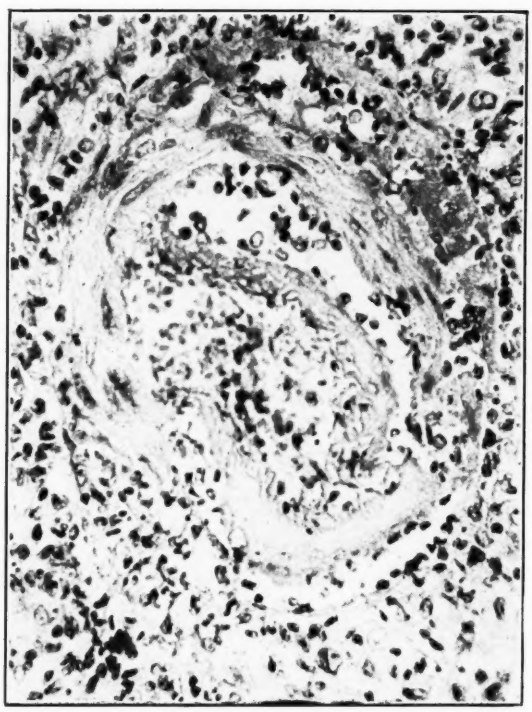

Fig. 2.—Section of artery of Fig. 1 (×200). Note recanalization of thrombotic vessel, thickening of vascular wall, and infiltration.

range, from 14,000 to 18,000; polymorphonuclears, from 76 to 80 per cent; eosinophiles, from 7 to 11 per cent. Sedimentation rate was 28 mm. in one hour. Chemical studies of the blood, including estimations of sugar, urea nitrogen, cholesterol, and serum proteins, were all normal. The blood Wassermann test was negative. Gastric analysis showed no free hydrochloric acid, but enzymes were present. The basal metabolic rate was +36.

The clinical picture was difficult to evaluate. We were not satisfied that the roentgen diagnosis of tuberculosis was responsible for the entire clinical picture. Toxic neuritis due to metal poisoning was excluded by a careful history. Avitaminosis was discarded when adequate doses of vitamin B_1 failed to ameliorate the neuritic pain. We could not discover evidence of malignancy anywhere. The stools were searched unsuccessfully for parasites to explain the eosinophilia. As the patient's condition became gradually worse, the diagnosis of periarteritis nodosa was suggested. This was based on the febrile course, the symptoms of polyneuritis and polymyositis, weight loss, eosinophilia, red blood cells in the urine, and, because of recent reports, the existence of asthma.

Fig. 3.—Section of kidney (×60). Note vessel thrombosis with necrosis.

In the course of the illness, a glandular enlargement appeared in the inguinal and axillary regions. Biopsy of an axillary gland showed no specific process; the architecture of the gland was only slightly altered by a moderate reticular cell hyperplasia. The report on a piece of excised muscle tissue was subchronic myositis.

In the last few days of her life, the patient showed confusion, neck rigidity, and a positive Kernig sign. The spinal fluid was under increased pressure but was otherwise normal. The temperature rose to 105° F., and the patient expired on June 22, 1936.

AUTOPSY

Heart.—Focal fibrosis was seen on section.

Lungs.—Multiple focal noncircumscribed lesions appeared, the great majority of which were located in contact with the pleura, infiltrating wedgelike the underlying parenchyma. The blood vessels showed periarterial infiltration with round cells. Purulent bronchitis and areas of lobular pneumonia were present.

Liver.—Normal grossly, but microscopically there were areas of focal hemorrhage and necrosis.

Adrenals.—The blood vessels in the soft tissues about the adrenals were thrombosed, infiltrated, and surrounded by lymphocytes and polymorphonuclear cells.

Kidneys were normal in size. Penetrating the surfaces of the kidneys were small, well-circumscribed, firm nodules and some poorly circumscribed grayish and hemorrhagic areas affecting chiefly the cortices.

Spleen was normal in size, firm, and plum-colored. No recognizable miliary lesions were seen.

Brain showed periarterial inflammation with round cells in both cerebral hemispheres. Sections from fat and muscle tissue of the legs showed endarterial thrombosis and periarterial inflammation with recanalization of arteries. The proximity of some of these lesions to nerves may have been responsible for an ischemic neuritis resulting in severe pain.

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Annual Review

ASTHMA AND HAY FEVER

Contributions During 1939

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THE year 1939 has brought to the open a number of contributions which should help to increase the intensity of the light beginning to permeate our understanding of asthma and hay fever and of allergy in general. It is our task again to review the events of the year in that field and to evaluate them critically. To that end it may be necessary from time to time to make comment on the procedure or interpretation of a particular piece of work. It is our earnest hope that such discussion will be considered free from any personal considerations. We are also particularly desirous to divorce ourselves from any claim to superior knowledge or judgment. Our comments will contain no more argumentative matter than we would present if we were to talk to each author personally.

Interest in the study of allergic diseases is spreading to the opposite side of the globe. Misawa[1] summarizes some of his observations and experiments in allergy in Japan. He says that hay fever is rare in Japan, but asthma and urticaria are common. Of the asthmatic patients, he could find only a small percentage who were allergic. In urticaria, however, allergic causes are common; most important of these are tuna fish, salmon, mackerel, and crab. Asthma due to food is not common. The results of his studies indicate that in allergy liver function is normal, that the blood groups have the same ratios as in nonallergic groups, and that sedimentation speed is within normal limits. During active asthma he found a 43 per cent reduction of phagocytic action of leucocytes. He has been able to produce attacks of asthma in asthmatic persons by the subcutaneous injection of from 0.5 to 0.7 mg. histamine. The same result was obtained with an extract of spinach. He believes that these methods can be used as diagnostic tests. Misawa has found that 5 c.c. of serum from a patient during an asthma attack, when injected into a guinea pig, causes a marked fall in temperature. He believes that, in a number of vegetables, such as spinach, eggplant, and bamboo sprouts, the exciting cause of allergic symptoms is a histamine or choline substance. He cites clinical and experimental results to substantiate this concept.

Service[2] has interviewed 1,000 families and 3,141 persons in Colorado Springs with regard to the presence of allergy and the types of manifestations. One of the interesting results of this survey was the discovery that more than 10 per cent of this number had hay

fever. More extended and periodic studies of this type are badly needed if we are to understand the clinical and public health problem facing us now and in years to come.

Vaughan's new book[3] on allergy contains an excellent summary of the available knowledge concerning asthma, hay fever, and similar atopic conditions. It constitutes a complete and detailed reference work for students of allergy.

MECHANISM OF HYPERSENSITIVENESS

The new industry of sugar beet cultivation in the Southwest has offered an opportunity for observations with regard to the time required for the production of hay fever by a new type of pollen. Sugar beet raising has become an active industry in the Phoenix (Arizona) region. In 1936 considerable acreage was given over to beets there. No observations were made during that year, but in 1937, Phillips[4] observed skin tests to beet pollen with no definite clinical manifestations. In 1938, tests were intensely positive, and many clinical cases were noted. In 1939, an equal number reacted to beet pollen, but the symptoms were less, because in many patients they had been controlled by treatment. The conclusion is reached that it takes about two years of exposure to a new pollen for the average person to become sensitive to it.

Shaw and Thelander[5] present the hypothesis that a deficiency of vitamin C may be essential to the production of hypersensitiveness as it occurs in infants. As argument for their concept, they cite a number of facts, such as: favoring of anaphylaxis in guinea pigs by the use of scurvy-producing diet; refractoriness to sensitization in animals which synthesize their vitamin C; relation of vitamin C to tissue permeability; the frequent lack of vitamin C in maternal blood, breast milk, and the artificial diet; and the restriction of spontaneous allergy to the only species, man, which destroys its vitamin C in the preparation of food (by cooking).

For many years attempts have been made to link the mechanism of allergy and anaphylaxis with the production of histamine or a histamine-like substance by the interreaction of antigen and antibody. Recently new impetus has been given to experimentation along these lines. Farmer[6] found that uterine strips of serum-sensitized guinea pigs that had received injections of histamine at the height of sensitization were less sensitive to the specific antigen than were the sensitized uterine strips of control animals. It was also found that histamine injections made the strips less sensitive to histamine. The suggestion is made that histamine is the substance responsible for the anaphylactic contraction of smooth muscle. Farmer,[7] in another series of experiments, showed that similar results could be obtained with histamine if the latter is administered orally to the animals.

Following the discovery of histaminase several years ago, it was but natural that hopes would run high for it as an agent in destroying histamine and counteracting the probable cause of anaphylaxis and allergy. This hope was soon shattered by the demonstration that histaminase would destroy histamine only if the two were mixed and incubated in vitro. More recent experimental work, however, again renews our anticipations of the possible usefulness of histaminase. Karady and Browne[8] found that the histaminase injection in guinea pigs fifteen minutes prior to the administration of lethal doses of histamine prevented shock from the latter in the majority of animals. In another series of animals which were sensitized to egg white, anaphylactic shock to the latter was almost entirely prevented by the administration of histaminase prior to the shocking dose of the antigen.

On the basis of the fact that the histamine substance is released at the site of the antigen-antibody reaction and that it would be expected to be found in greatest concentration there, Ertl[9] conceived the idea of local treatment with histaminase in hay fever.

A recent experiment recorded by Abramson and his associates[121] is offered as an argument against the histamine mechanism in allergy. These workers have developed an iontophoretic method of detecting histamine in dilutions as high as 1:5,000,000 by the formation of wheals in human skin. If the negative pole is applied to the surface of a wheal produced by histamine, a sufficient quantity of this chemical is transported by this reversal of iontophoresis to form secondary wheals in new areas of the skin. Histamine has been reversed from wheals which have been produced by iontophoresis from original dilutions as high as 1:100,000. This method was used in attempting to obtain histamine from wheals formed by ragweed, timothy, ultraviolet light in cases of urticaria solaris, and wheals produced by stroking in a case of dermographism. In none of these instances was histamine demonstrated by reversed iontophoresis.

Much work, observation, and experimentation will have to be done before the histamine mechanism of allergy can be accepted and, as a corollary, the histaminase treatment of allergy. Space does not permit a full discussion of the objections to the explanation of histamine as the usual agent producing allergic symptoms. One needs to be reminded only that the clinical manifestations of allergy cannot be entirely explained on the basis of histamine action.

ETIOLOGICAL CONSIDERATIONS

That nonpollen factors may produce seasonal allergy is re-emphasized by Prince.[10] Among such nonpollen causes he lists fungi, animal danders, orris root, and foods. A high incidence of reactions to fungi was observed in the summer group.

Coles,[11] of Ames, Ia., has found a large number of spores of *Alternaria*, *Hormodendrum*, rust, and smuts on her slides throughout the summer and fall. She believes that these spores may play an important role in the causation of respiratory symptoms. Halpin[12] (Iowa) also finds fungi as a cause of allergy and considers *Alternaria* and *Hormodendrum* of marked importance. Rackemann[13] has obtained intracutaneous reactions with fungi in 36 per cent of 60 asthmatics. Apparently, Rackemann is beginning to express doubt in his previous view of a high order of species-specificity among the fungi.

The smuts are beginning to demand their place among the fungi as recognized causes of allergy. Wittich[14] emphasizes the high incidence of smut spores in the air of Minnesota and the Northwest. These smuts originate from infected grain and are abundant from July to November. He believes that allergy to smuts is responsible for a great number of the respiratory symptoms in his territory. Almost all smut reactors also react on test to other air-borne fungi. Wittich finds that there is a tendency for the smut-sensitive person to react to the host grain from which the smut originated.

For many years, in our slide observations of the Chicago atmosphere, we had noticed smut spores. However, they do not appear to occur in extraordinary numbers, although we have not made systematic counts. It is of interest to note that Blackley, in his classic book on hay fever published in 1873, observed the smuts on his slides and mentioned spore counts of *Ustilago segetum* of 6,000 or 7,000 per square centimeter. We have obtained numerous skin reactions to smut, but almost never were the fungus reactions confined to that group.

Harris[15] reports thirteen cases of allergy to grain dusts and smuts. Most of the patients were farmers or lived on the farm. All of them gave a history of symptoms after exposure to grain dusts. Many of them also had inhalant allergy caused by ragweed pollen or fungi found in the general atmosphere. As additional evidence for the etiological relationship between grain dusts and smuts, Harris offers several observations. Positive skin tests to grain dust and smuts were obtained in all cases. Reagins to grain dust and to one or more smuts were found in the seven cases examined for them. Instillation of the dusts or smuts into the nose caused clinical reactions, while an occasional constitutional reaction occurred from subcutaneous injection. In a limited number of patients in whom treatment was given with grain dust, benefit was obtained.

Hultborn[16] warns of the possible dangers of injections of contrast medium for urography. In seven of his cases, allergic reactions occurred, which in four were associated with shock. In four of the patients, a history of previous allergic symptoms could be obtained. He

cautions against the use of intravenous contrast medium in allergic persons.

A case of asthma and rhinitis in a chemist was traced to phthalic anhydride.[17] Positive scratch reaction and good passive transfer were obtained. This case is of interest because of the skin reaction obtained with a chemical of this order and because of the relationship of this substance to naphthalene, or camphor flakes and balls.

What is apparently allergy to wood smoke is described in the case of a fireman reported by Rappaport and Hecht.[18] It may be said that, with the exception of the failure to obtain positive skin tests, which finding may be in entire agreement with the possibly simple chemical nature of the antigen involved, the various observations of the authors would indicate that this case is one of true allergy to the smoke.

In this connection we are reminded of a passage in one of the classic treatises on asthma by one of the fathers of allergy. In his book *A Treatise of the Asthma,* published in 1698, in discussing some of the causes of asthma, Sir John Floyer says: "I always observ'd the Smoak of Wood more Suffocating than that of Coal, and more apt to occasion a Cough." In connection with mold and grain dust allergy, we find in the same book the following pertinent bits: "There is a Remarkable Instance in *Borretus* of an Asthmatic, who fell into a violent Fit by going into a Wine-Cellar, where the Must was fermenting. . . ." Another passage states: "The Sensibleness of the Trachea is very evident: because all Asthmatics are offended by the least Dust made by Sweeping a Room, or making a Bed. I knew one, who was a Maltster, who told me, he could not bear the Dust of Corn whilst it was removed."

The histories of three patients having asthma from sulfur dioxide fumes from refrigerators are cited by Romanoff.[19] This gas is an irritating chemical and, like coal smoke, wood smoke, and other irritating gases, it may precipitate asthmatic attacks in persons who are basically sensitive to other allergens. These gases are probably, in the majority of instances, to be regarded as secondary, and not primary, causes. This distinction is important to keep in mind in the interpretation of cases of a similar character.

Seasonal asthma due to pine pollen is reported by Rowe.[20] There is something about pine pollen which places it in the class of poor allergens, and, therefore, this report does concern an unusual case. Sugar beet *(Beta vulgaris)* pollen is apparently an increasing cause of hay fever in the Southwest. While it belongs to the *Chenopodiales* and tends to interreact with other chenopods, such as Russian thistle, Phillips[4] thinks that it has an atopen of its own.

The common clinical observation of the influence of weather changes on the asthmatic state was made the object of a study in the experimental animal. Preuner[21] sensitized guinea pigs and then produced

various grades of anaphylactic and asthmatic reactions in them by vaporizing the antigen. It was found that, during periods of rapid meteorologic change, the severity of the symptoms was increased by about 50 per cent. This method of study may constitute an approach for investigation of various relationships between weather and allergy.

The psychiatric point of view as a basis of asthma is still satisfying to some psychoanalysts.[22-24] To one who has observed for long periods of time many hundreds of asthmatic patients under varying conditions of seasons, weather changes, and other vicissitudes of life, the reports concerning the primary importance of psychic factors lack the necessary convincing evidence. We would accept them as proof of the importance of the psychic factor if, in case of such definitely demonstrable and reproducible allergy as pollen sensitiveness, attention to the psychic difficulties would keep the patient from an attack if exposed to that pollen.

ATMOSPHERIC OBSERVATIONS

Local air studies with reference to pollen and fungi continue to increase. Sylvester[25] corroborates his previous finding of the ragweed situation in Maine. Although in parts of the state the total pollen counts for the season ran as high as 526, it was only 57 in Aroostook County. Metzger[26] discusses the hay fever situation in Florida. Grass pollen causes comparatively little trouble, and Bermuda grass is the most important in the group, pollinating from March to July. Of the trees, the oak is the most important. The pecan and eucalyptus are also important trees as causes of hay fever. The ragweed counts in Florida are very low, although, due to more building and road construction, the amounts are increasing. The ragweed season varies in its inception from the first part of May to the middle of August. All the ragweeds are dead by the middle of November.

An atmospheric survey of Nashville (Tenn.) was made by Bowie[27] for 1936 and 1937. Grass pollen was found in small quantities from spring until frost. Among the species observed were blue grass, orchard grass, Bermuda grass, Johnson grass, and others. The trees pollinate in the spring in approximately the following order: elm, beech, hackberry, oak, hickory and walnut, machura and mulberry. The most important cause of fall hay fever is ragweed, and pollination begins about the middle of August. Other fall pollinators are: annual wormwood (*Artemesia annua*), lamb's-quarters (*Chenopodium album*), Mexican tea (*Chenopodium ambrosioides*) and Jerusalem oak (*Chenopodium botrys*). The fall-flowering elm (*Ulmus serotina*) is an important pollinator in September and October.

The hay fever situation in Hawaii is described by Roddis.[28] He finds that the tropical plants, in general, produce such large and sticky

pollen that they seldom become a problem. The pollens most frequently giving trouble are redtop grass, algarroba, Bermuda grass, date palm, royal palm, sugar cane, and mango. Nevertheless, the total pollen counts are never high. The hibiscus flower which the women commonly wear in their hair is the cause of some cases of allergy. In the discussion of this paper, H. P. Larsen corroborates the finding of low pollen counts in Honolulu, but mentions a black spore from a fungus showing a high count in many places and giving positive skin reactions.

Hara[29] made pollen studies of Tokyo and Kobe from March to November, 1936. The pollen counts were very small, and pollen was found from the end of March until the end of May. Pine pollen constituted the greatest part of all pollen found. Ragweed has been unknown in Japan, but Hara believes that it is gaining a hold in that country. The pollen survey of Japan explains the almost complete absence of hay fever there.

In Cuba, Cadrecha and Quintero[30] have made an informative study of the hourly variations in atmospheric mold spores in relation to meteorologic influences. They found a larger number of spores during the daytime, with *Hormodendrum* predominating. Increases in barometric pressure, temperature, or wind velocity increased the spore counts. In their clinical work, these authors have attached greatest importance to *Hormodendrum*, *Mucor*, *Penicillium*, and *Alternaria*.

ANTIGEN AND ANTIBODY STUDIES

House Dust.—The status of the antigen in house dust continues to occupy the attention of investigators. Buffum and Freedman,[31] on the basis of dust and other inhalant reactions in children and on the basis of results of treatment, are inclined to agree with Walzer's concept that the dust atopen is only a composite of the other known household inhalant atopens. Cohen has always insisted that the house dust antigen is specific, and, now, with his co-workers,[32] he presents additional evidence for that contention. A dialyzed linters extract, which in 1:50 dilution gave specific reactions on dust-sensitive persons, was injected into guinea pigs. Anaphylactic reactions followed on reinjection. That the active principle of this extract is not cottonseed is indicated by the fact that when 1:100 cottonseed extract was used on reinjection no reactions followed.

Friedman[33] sensitized guinea pigs with 1 per cent alum-precipitated house dust extract and obtained anaphylactic reactions on intravenous reinjection with regular house dust extract. The Dale test was also positive. By the uterine and intestinal strip method, it was shown that the contractility was not due to histamine. Anaphylactic death could not be induced with less than 0.1 c.c. of the dust extract, while doses of more than 1.0 c.c. caused anaphylactoid reactions.

The problem was also tackled by Coulson and Stevens[34] who performed experiments on guinea pigs with undialyzed extracts of linters and house dust. With linters on the first injection no symptoms occurred, whereas the second injection caused from moderate to fatal anaphylaxis. House dust samples varied in their behavior. With one type, practically no symptoms occurred on the first injection, but typical anaphylaxis resulted on reinjection. With another specimen, considerable anaphylactoid symptoms, even fatal ones, occurred on the first injection.

From the above reports, it becomes clear that dust has an antigen, and probably one that is specific for dust. It is also apparent that, in addition, dust has a toxic principle (histamine?) which varies in content in different specimens. It is probably the confusion of the toxic and allergenic qualities of house dust which is responsible for such discrepant clinical reports.

Cohen[35] comments on the usefulness of a relatively simple apparatus for the lyophilization of dust and pollen extracts.

Studies on the relationship of the smuts to grain dusts by means of cross-desensitization methods were made by Harris.[36] It was found that wheat dust and oat dust neutralized each other's reagins both in vivo and in vitro. Wheat dust neutralized the wheat reagin, but wheat did not neutralize the wheat dust reagin. Mutual reciprocal neutralization was obtained between wheat dust and wheat smut, and also between oat dust and oat smut. No cross-desensitization occurred between the dust extracts and the common molds. Cross tests between the various smuts resulted in some neutralization, but the results were not always complete or reciprocal, indicating that the smuts do not all have a common antigen. The work of Harris is extremely important and stimulating. The inference is there, even if not expressed, that an organism takes on the antigenic structure of the host upon which it grows. A great deal more work along this line is necessary. It may be that this principle applies only to the type of organism which destroys or consumes the tissues of the host. Whether or not this same finding applies to other types of fungi or plant life remains to be determined. In the light of past experiences, it is open to doubt.

Pollen Studies.—The chemistry and the antigen of pollen are receiving their due attention. Stull and Sherman[37] prepared proteins of ragweed pollen by ammonium sulfate precipitation, dialysis, or precipitation with alcohol and ether at –10° C. Proteins prepared by these methods neutralized the skin-sensitizing antibody of ragweed-sensitive serum at about the same strength as whole extract, if all materials were adjusted to contain the same amounts of protein nitrogen. The nitrogen going through the dialyzing membrane was

shown to be unable to neutralize the skin-sensitizing antibody. The dried protein precipitated with alcohol and ether was redissolved ten months later and found to be almost as active as fresh extract. Using similar methods of study, they found that ragweed extract at the end of ten months showed a loss of protein and that the remaining protein showed a marked loss of neutralizing capacity.

Eagle and his co-workers[38] broke up several varieties of pollen in a special ball mill at a temperature of –80° C. Despite the fact that there was a higher total nitrogen and higher protein fraction than in extracts prepared by the ordinary methods, immunologic and clinical studies failed to show any appreciable differences. It was shown by Gelfand and his associates[39] that filtration of pollen extract by vacuum causes a loss of the CO_2 in the solution, which causes a precipitate resulting in considerable loss of protein nitrogen and activity of the solution. Some of the ragweed antigen is adsorbed on the precipitate.

The stability of pollen extracts is the object of several studies. Sullivan and Vaughan[40] prepared a 10 per cent ragweed extract with glycerosaline and found that it contained fully five times the potency of a 2 per cent extract, as determined by the end point in intradermal testing. The protein nitrogen, however, was only slightly more than three times the amount. After eighteen months in a refrigerator, 10 per cent glycerosaline extract was more potent than 2 per cent extract or 10 per cent dextrose extract. Curiously enough, the 2 per cent dextrose extract was more potent than the 10 per cent extract.

A reliable method of assaying and comparing the potency of antigens has been the goal of many workers. Arbesman and Eagle[41] say that protein determination, complement fixation, direct dilution testing by cutaneous or intracutaneous methods, and passive transfer testing are all objectionable methods. They believe that the relative activity of ragweed pollen extracts could be ascertained by the determination of the minimal concentration of extract necessary to neutralize a homologous reagin. To twofold dilutions of pollen extract are added 0.2 c.c. quantities of reagin serum. The mixtures are incubated, and 0.1 c.c. amounts are injected intracutaneously into recipients. In from twenty-four to forty-eight hours each site is tested with 0.01 c.c. of pollen extract in a dilution of 1:100. The amount of each extract which suffices to prevent passive sensitization, as evidenced by a negative reaction, is taken as its neutralizing concentration. Similar results were obtained by neutralization in vivo. The authors admit that this method has an error possibility of from at least 50 to 100 per cent. Is not this method in reality a passive transfer titration in which the titer of reagin is diminished by previous partial neutralization?

Using the above method, the same authors[42] found that about 90

per cent of the potency of ragweed extract is destroyed after exposure to a temperature of 56° C. for one hour. Extracts stored at icebox temperature since 1929, 1933, and 1937 were compared with 1939 extracts. The relative respective potencies, on the basis of 100 for the 1939 extract, were 1.2, 4.5, and 16. Despite these marked changes in potency, the protein nitrogen contents and the ratios of protein nitrogen to total nitrogen were essentially the same as in fresh extracts. The thermolability of ragweed reagin was determined by the ability of a 1:100 extract to react in sites injected with dilutions of heated reagin. The percentages of reagin destroyed at 56° C. were as follows: one-half hour, 50 per cent; two hours, 90 per cent; and four hours, 99 per cent.

Making use of their previously described method of comparing skin reactions, Efron and Dorfman[43] demonstrated how dust extracts of varying concentration and varying potency can be evaluated. The method consists of grading the reactions of decreasing concentration (from 100 per cent to 1 per cent) of dust extract on several scratch tests, using one side of the forearm for the test material and the other side for the material with which it is to be compared. By this means they found that skin reaction curves to house dust are discontinuous, i.e., reactions of equal size occur at wide ranges of concentration. Reactions of greater size denote greater potency.

Abramson and Gorin[44] have described a gauge which aids them in recording the horizontal and vertical contour of wheals.

Hampton and his associates[45] investigated by the Dale technique the antigenic relationships in the guinea pig between short and giant ragweed and between timothy, orchard grass, and June grass. Guinea pigs were sensitized by a single intraperitoneal injection of 2.5 c.c. of washed alum-precipitated pollen extract, 25,000 protein nitrogen units per cubic centimeter. After a lapse of three weeks or more the animals were killed and tests on uterine strips were performed. The related pollen extract always produced a contraction of the uterine strip sensitized to the specific antigen. However, neutralization of the uterine strip by the related pollen, so that it would not react to the addition of the specific antigen, occurred only in twenty-one out of thirty-eight instances. The specific pollen extract always neutralized the strip to the related pollen extract. These experiments corroborate previous findings by other methods of an antigenic relationship, but not an identity, of the related pollens used.

Prince and Secrest[46] studied the immunologic relationship between several ragweeds and marsh elder (*Iva ciliata*) by the method of cross-desensitization of serum containing reagins to both. Their technique was to test passively sensitized sites with 0.25 c.c. of a 1:1,000 protein unit strength of pollen extract after the former had been previously

desensitized by a heterologous pollen. In sites desensitized to *Iva ciliata*, ragweed gave no reaction. In the reverse experiment, however, *Iva ciliata* gave a marked reaction. The authors conclude that marsh elder pollen contains an allergen not present in giant, western, or common ragweed pollen. This conclusion is not justified from the recorded experiments, since, by previous direct transfer tests, they showed that marsh elder reactions are obtained in much higher dilution. The results of these workers may merely indicate, irrespective of comparable protein concentrations, a marked difference in the quantity of the antigenic material in, or a marked variation in the relative sensitivity of the patient to, the antigens compared.

The question of specificity was also reopened by Rowe and Fong,[47] who made cross-precipitin tests on guinea pig serum from animals inoculated with a variety of grass pollens. They found positive precipitin reactions only in those sera tested with the species of grass extract used for sensitizing and no reaction for the other grass pollen extracts. The authors do not give any results as to titer. These findings are so contrary to the numerous researches on specificity with the precipitin test that it should encourage a reinvestigation of the entire field.

And now appears a preliminary report of the work of Winkenwerder and his associates,[122] giving supporting evidence to the concept that the same antigens may be obtained from totally different sources. These authors found that persons who react to ragweed pollen extract also give positive reactions to dilute solutions of nucleic acids and many of their derivatives. Only an occasional reaction was observed in a series of forty nonallergic control cases. A skin-sensitizing antibody to yeast nucleic acid and related compounds has been demonstrated in the sera of ten persons reacting to these compounds.

Other Experiments on Antibodies and Antigens.—By means of the Tiselius electrophoresis apparatus, Newell and his associates[48] fractionated human allergic serum into the albumin and the alpha, beta, and gamma globulins. By passive transfer tests the skin-sensitizing antibody was found to be present in the gamma globulin fraction. The antibody for ragweed in rabbits was also found in the same fraction. No antibodies could be demonstrated in the other fractions.

The fate of reagins in transfused blood was studied by Garver[49] by the transfusion of 500 c.c. amounts from two allergic donors into three recipients. After transfusion, reagins could be demonstrated by direct skin testing. The sensitivity of the skin to the allergens was maximum in four or five days and remained for about two weeks. After that the reactions were uncertain. No clinical tests or observations were made.

Eagle and his co-workers[50] found that rabbits sensitized to various forms of pollen preparations by intra-abdominal, intracutaneous, or

intravenous injections three times weekly over a four-week period, regularly produced precipitins and complement fixing antibodies. Guinea pigs could be passively sensitized with serum from these rabbits. Active sensitization in guinea pigs was easily attained by a single intra-abdominal injection of the pollen preparation. In another experiment[51] these workers found that rabbits sensitized by the above methods produced sera which would successfully sensitize normal human skin. The methods of sensitizing the rabbits varied in their ability to produce this transferable antibody; the subcutaneous route was the most efficient, while the intravenous was the least productive.

Sherman and his associates[52] were also able to sensitize human skin with serum from guinea pigs which had received, two to four months previously, a single intra-abdominal injection of alum-precipitated pollen extract. The intensity of the reactions obtained upon testing with the homologous antigen was in no case as great as that produced by sera of actively sensitive humans. None of the sera of the animals bled less than two months after the injection passively transferred sensitivity to the human skin.

Newell[53] has made a contribution to the question of the physical relationship between antibody and antigen in the blood. By means of the air-driven ultracentrifuge and the Tiselius electrophoresis apparatus, he studied mixtures of antigen and serum from a person sensitive to rabbit hair and rabbit serum. Under the conditions of the experiments, no evidence of physical reaction between the antigen and antibody could be found.

Sinclair and Thomas[54] studied the heterophile antibody in allergic and nonallergic patients. In 107 nonallergic people, the titer was high (above 1:16) in 11.2 per cent. In allergic patients with blood taken at any time, but usually in the inactive stage of the allergy, an increased titer was found in 37.7 per cent of 114 cases. In thirty-four cases, blood taken during allergic activity showed a high titer in only 6 per cent.

A singular contribution has been made by Karady[55] to the often-debated possibility of the production of antigens from one's own tissues. This investigator exposed guinea pig serum to cold (–5° C.) or to heat (56° C.) for one and one-half minutes and injected it into normal guinea pigs. The reinjection of similarly treated serum three weeks later produced typical anaphylaxis, but no anaphylaxis resulted when the serum injected had been exposed to the opposite physical condition. Similar results were obtained by sensitizing the animal by the exposure of its hind legs to cold or heat. Furthermore, both the sensitization and the shocking could be produced by exposing the hind legs of the animal to the thermal change. In all of these experiments, cross exposures gave negative results. The author concludes,

"The present experiments seem to indicate a new mechanism in the production of physical allergies by which the organism's own protein can be changed by various physical agents, such as heat and cold, so that it acquires antigenic properties and becomes in our terminology an 'autoantigen.'"

The results of these experiments have such far-reaching propensities that their corroboration and extension will be awaited with great interest. In the meanwhile, we merely wish to note that they seem to be contrary to clinical observation. If we behaved like Karady's guinea pigs, all of us living in the temperate zone would be expected to become sensitive to cold. As a matter of fact, it would seem to us that many a guinea pig must have been naturally exposed to such low temperatures as described in the experiments. And yet anaphylactic reactions in guinea pigs exposed to weather changes must be far from a common phenomenon.

CONSTITUTION AND METABOLISM

The progression of allergic symptoms in the child from birth and the interference to facial growth resulting from this constitutional disease are processes described by Cohen[56] to orthodontists. Of chief interest to the latter is the high narrow dental arch, the protrusion of teeth, and the malocclusion resulting from poor bony growth. The author points out that proper allergic therapy begun early may prevent these orthodontic deformities. The reviewers have been observing for several years these changes in the face and, particularly, in the jaws, and agree wholeheartedly with Cohen. Even before malocclusion occurs, it is interesting to note how often one can recognize the high palate as an indicator of long-standing nasal allergy and as a forerunner of orthodontic deformity.

Blood changes during allergic shock as a result of overdose of pollen extracts were studied by Waldbott and his associates.[57] The blood sugar showed a mild immediate transitory rise, followed in about fifteen minutes by a marked fall from an average 80 mg. level to 55 mg. The blood pressure showed a marked systolic and diastolic fall. The white blood count dropped also. The eosinophile count was of no aid, according to Hunt,[58] in differentiating between intrinsic and extrinsic asthma. Thiberge[59] presents data on blood platelet counts in allergy and concludes that an allergic spell is indicated by a drop of platelets in the circulation, while improvement is indicated by a marked rise in the count. His figures, tables, and the absence of proper controls make one skeptical of the propriety of the interpretations.

In twenty patients with acute and chronic asthma, Rusk and his associates[60] found an increased serum potassium during the asymptomatic stage, which was further augmented during the attack. The

potassium-lowering effect of insulin, glucose, and epinephrine was corroborated by these workers. That the insulin effect was not due to hypoglycemia was shown by the fact that the administration of glucose prior to insulin injection did not prevent the lowering of the potassium level.

Sheldon, Howes, and Stuart[61] have made a valuable contribution to the study of the metabolism of asthma. Under hospital conditions and with standardized diets and environment, they measured the water and sodium exchange in patients during induced attacks of asthma. In attacks lasting at least twenty-four hours, it was found that there was a definite loss of body fluids, chiefly by the urine, and that the urinary sodium was correspondingly increased. The total heat production was not increased appreciably, and the loss of body weight was due almost entirely to the loss of body water. The authors do not venture an opinion as to whether these changes are due to the asthma or are, in some way, responsible for it.

CLINICAL MANIFESTATIONS

Kahn[62] reports a case in which a unilateral facial acne resulted following a positive diagnostic intranasal pollen test made on the same side, and which reappeared on the sensitized side on four different occasions in the course of specific treatment.

The belief is expressed by Balyeat and Seyler[63] that, in almost all cases of intractable asthma, a dual etiology exists, the sensitization factor and the mechanical factor. The mechanical factors are equally important and consist of mucus plugs, purulent bronchial secretions, and bronchiectasis. Watson and Kibler[64] present evidence supporting the importance of the role of allergy in bronchiectasis. In forty-six cases of the latter, they found 63 per cent of the patients with sinusitis, 82 per cent with positive skin tests, 58 per cent with nasal allergy, and 32 per cent with asthma. About 72 per cent showed bronchial or nasal secretion, in which 10 per cent or more of the cell contents were eosinophiles. The authors believe that bronchiectasis can be favorably influenced by allergic management.

In a group of eighty-three consecutive cases of asthma and asthmatic bronchitis, Prickman and Moersch[65] found bronchostenosis as a common complication. The symptoms which should arouse suspicion of a bronchostenosis are persistent, wheezing cough, blood-streaked sputum, and bouts of chills and fever with leucocytosis. The physical findings, when present, are those of atelectasis and may be unilateral. Roentgenologic findings are those of atelectasis or bronchiectasis. The diagnosis of stenosis is definitely made by bronchoscopy. Treatment consists of dilatation of the stenosis and aspiration of the retained secretions, in addition to postural drainage and allergic management.

Friedman and Molony[66] also discuss the relation of allergy to atelectasis. In seven allergic children atelectasis occurred during an asthma attack, spontaneously in six and postoperatively in one. They also believe that such atelectatic changes are due to bronchial occlusion, but they blame bronchospasm, thickening of the bronchial walls, tenacious sputum, and paradoxic collapse of the bronchi as the causes. The treatment is essentially the same as that recommended by Prickman and Moersch, except that dilatation of the bronchi is not mentioned.

Rackemann and Greene[67] described eight patients in whom the syndrome of severe asthma, pain and numbness of the extremities, and a high eosinophilia, ranging from 25 to 80 per cent, was present. These cases were later diagnosed as periarteritis nodosa. Four of these patients died. The authors suggest that, with the presence of the above findings, a diagnosis of periarteritis nodosa be assumed and a bad prognosis made.

Löffler's disease, first described by Löffler of Switzerland in 1932, is receiving increasing interest. Söderling[68] reports three cases in children with asthma and asthmatic bronchitis. The characteristic features were transient lung consolidations appearing during the course of the disease, associated with marked eosinophilia in the blood or sputum and rapid spontaneous clearing of the consolidations. Bezancon and his associates[69] describe two similar instances. Smith and Alexander[70] report in detail the case of a child who had lung infiltrations associated with eosinophilia. The fatal outcome and the blood findings throw considerable doubt on the identity of this case with Löffler's syndrome. The blood changes are certainly more suggestive of leucemia.

No doubt the wheezing caused at times by bronchiogenic carcinoma is mistaken for bronchial asthma. We have had occasion to see that happen several times. Lockwood[71] points out that the finding of wheezing may be an early sign in bronchial carcinoma, especially when it is accompanied by cough and occasional blood-streaked sputum. This wheeze is continuous and best heard at the end of expiration.

One of the most troublesome questions in the practice of allergy is the differentiation of cardiac from allergic asthma. Plotz[72] succinctly states that the usual methods of differentiating between bronchial and cardiac asthma are not always reliable. One might emphasize that statement further by saying that nothing much has been added to the clinical differentiation recorded as early as 1698 by Sir John Floyer. However, a study of the circulation time constitutes a definite advance in this field. Plotz finds that, in the cardiac type, the circulation time shows a decreased velocity in the pulmonary

circuit, while in allergic asthma this circulation is actually increased. His method of measuring the left heart time is to subtract the arm-to-lung time (intravenous injection of 0.3 c.c. of ether with 0.3 c.c. of salt solution) from the total circulation time (sodium cyanide). Gubner and his associates[73] suggest a more simple and harmless method of measuring the left heart time. The patient takes two deep inhalations of 50 per cent carbon dioxide. The end point is the sensation of warmth over the head and the quickening and deepening of the respiration. In normal persons this circulation time was from 5 to 10 seconds, the majority being from 7 to 8 seconds. In cardiac failure the time was increased, the increase being proportional to the degree of left heart failure. The four asthmatic patients without heart disease had normal values for circulation time.

EPINEPHRINE AND OTHER PALLIATIVE REMEDIES

One of the worth-while recent advances in the therapeutics of allergic manifestations has been the development of a slowly absorbing epinephrine preparation. Keeney and his associates[74] used epinephrine base suspended in peanut oil, so that 1 c.c. of the suspension contained 2 mg. of epinephrine. They found that from 0.65 to 2.0 c.c. of this suspension gave relief for from eight to sixteen hours. They also emphasized the fact that the undesirable actions of epinephrine, such as nervousness and tachycardia, are lessened. In a later communication, Keeney[75] cites his results with this material in a greater number of cases and emphasizes the fact that relief occurs often for as long as twenty-four hours. He also advises the preliminary use of aqueous epinephrine hydrochloride in acute asthma. Murphy and Jones[76] confirmed, in general, the findings of Keeney and his group. Our experience with this form of therapy indicates that it has a sphere of usefulness. It is particularly efficacious if, in the severe and frequently recurring attacks, the asthma is at first relieved by the usual epinephrine solution and then followed (in about thirty or forty-five minutes) by an injection of the suspension in oil. If this precaution is not used, the suspension will frequently fail to result in relief. In status asthmaticus we have not been so fortunate as to obtain the extent of duration of relief described by others. It is also noticeable that with continued use of the oil a soreness and induration may develop. Whether this is a form of induced allergy has not been determined.

Another preparation of epinephrine for slow absorption has been advocated by Spain and his co-workers.[77] This consists essentially of epinephrine suspended in a solution of gelatin. The claims made for this material are practically identical with those claimed for the oil suspension.

Cohn[78] describes four cases in which epinephrine in peanut oil gave untoward reactions. One patient developed an allergic dermatosis,

two had symptoms resembling shock and accompanied by vomiting and chills, and another developed a very marked, spreading local reaction. Keeney[79] reports the production of what appears to be a hemorrhage involving the cortex of the inferior parietal region, following the injection of 0.5 c.c. of 1:1,000 epinephrine hydrochloride. Although the patient was known to be free from hypertension prior to the injection, Keeney feels that the hemorrhage was due to sudden high blood pressure resulting from the injection of the epinephrine into a small blood vessel.

Graeser[80] found, by experimenting with various concentrations of epinephrine by inhalation, that 1:100 strength was the most efficient and the safest. Many other inhalants, such as 10 per cent ephedrine, 5 per cent neosynephrine, or epinephrine to which posterior pituitary solution was added, were of no benefit.

By weighing epinephrine vaporizers before and after use, Galgiani and his co-workers[81] found that not more than 0.08 mg. of the drug is received into the mouth after ten inhalations. Previous investigators had found that only about 3 per cent of the vapor reached the lungs. Epinephrine solution was applied to three different portions of the respiratory tract of cats—to the mouth and nasopharynx, the trachea, and the bronchial airways. Pressor effects were only obtained from the application of epinephrine to the bronchial mucosa. Since, clinically, the amount of epinephrine reaching the bronchi is very small, the experiments indicate that the antiasthmatic effect of inhaled epinephrine is due to direct local action on the bronchi. Continued spraying of the epinephrine into the respiratory tracts of cats and rabbits resulted in some of them in the loss of tracheal cilia, desquamation of tracheal and bronchial epithelium, tracheitis, and bronchitis. The authors warn against the possible dangers of epinephrine sprays.

A series of ten patients with severe asthma was treated by Abramson[82] with the electrophoretic administration of epinephrine phosphate. A single treatment consisted of the application to two or three areas, each being treated for from ten to fifteen minutes. The results were at least equal to those obtained by the subcutaneous administration of 5 minims of 1:1,000 epinephrine. The author believes that the local blanching effect produced allows large doses to be administered, while the rate of absorption is slow. Consequently, symptoms may be relieved for longer periods of time than by the injection method.

On the basis of the experimental results obtained in anaphylaxis and on the sensitized uterine strip, Farmer[83] employed urethane in a small group of cases of asthma and obtained relief with doses of from 1 to 2 Gm. dissolved in water and given orally. Meyer and Schotz[84] describe dramatic relief in a patient with intractable asthma by the use of cyclopropane anesthesia.

Balyeat,[85] in conformity with most authors, warns against the use of morphine in asthma. He describes five fatal cases in which he believes that morphine was mainly responsible for the outcome. The dangers of narcotics cannot be overemphasized in spite of the fact that they are useful occasionally. Salter, in 1864, warned against the use of opiates in asthma, and gave good logical reasons for his admonition. Ramadge, in 1835, said that narcotics might be efficacious in the beginning of the attack, but might aggravate the condition when congestion was marked. Sir John Floyer, in 1698, mentioned the dangers of narcotics. It is about time that we begin to learn!

Kalmon[86] found benzedrine base inhaled orally to be moderately effective in light asthma attacks, but not in the severe seizures. This method was not as effectual as epinephrine inhalations. Propadrine hydrochloride was found by Murphy[87] to be as efficient as ephedrine in the relief of allergic conditions. It had the added advantage that untoward effects were minimized with this drug. While the reviewers have found this drug useful as a substitute, particularly in those who cannot tolerate ephedrine, the impression is gained that its effectiveness cannot be compared with that of ephedrine.

Parkinson[88] recommends the use of an ephedrine solution which is of the same hydrogen ion concentration as the nasal secretion, so that mucosal shrinkage will be obtained without irritation. In addition, he advocates applying vasoconstrictor drugs to the nose by the use of the lateral head-low posture, which consists of the patient lying on the side, with the head bent downward exactly sidewise, using the shoulder as a fulcrum.

Theophylline ethylenediamine has received approbation again in the treatment of bronchial asthma, this time from Efron and Everett.[89] We agree with the claims of these authors, but also admit that we frequently fail to get results with this drug. We have been particularly puzzled by the observation that in the same person we encounter different series of attacks which respond in varying manners to the administration of this drug. Curiously enough, the impression is gained that, in the same patient, a severe status asthmaticus is actually benefited more than an ordinary acute attack. Since this drug has been shown recently by Young and Gilbert[90] to exert marked bronchodilator action on the bronchi of guinea pigs, the above clinical observations may possibly have an explanation. Perhaps this is a clue to the likelihood that in early and ordinary asthma the mechanism of the dysfunction is due to obstruction from edema of the mucosa, while only in the more severe and lasting attacks, a spasm of the bronchial musculature follows.

POTASSIUM SALTS AND ORAL POLLEN

The tedious and painstaking diagnostic and therapeutic details necessary in the management of allergic diseases have stimulated many physicians to wish for a little pill which might simply be swallowed by the patient and would then properly correct all his maladjusted tissues. And thus it is that Bloom's original recommendation of the use of potassium chloride in allergic diseases has swept like a whirlwind through the medical world, the pharmaceutical trade, and, thanks to the newspapers, the public at large.

Another paper has appeared by Bloom and Grauman.[91] This reports relief in forty-eight of fifty-two cases of hay fever, seven of nine cases of pollen asthma, thirteen of twenty cases of "chronic allergic sinusitis," four of seven cases of nasal mucous polyps, seven of eight cases of acute urticaria, two of three of chronic urticaria, two cases of angioneurotic edema, five of eight cases of eczema, and two of eight cases of migraine. In only one type of allergy did they make a poor showing; in chronic asthma they were able to relieve only two of twenty-nine cases. One of the difficulties with evaluation of such work as reported in this paper is that there are no indications as to what kind of hay fever was treated, when the patients had symptoms, what the pollen counts were, and many other bits of evidence which should support the claimed results.

In a communication to the editor of the Journal of the American Medical Association, Engelsher[92] stated that he had administered potassium chloride to sixty-four patients with allergy, including cases of tree and grass pollinosis, angioneurotic edema, and asthma. Not only did Engelsher fail to obtain beneficial results, but many of his patients reported toxic and, particularly, gastrointestinal symptoms. To this comment Bloom[93] replied in another letter that the gastrointestinal symptoms were due to the erroneous technique of using tablets instead of a solution of the salt. The lack of therapeutic results in Engelsher's patients is not explained by Bloom, but he quotes Abt's paper in substantiation of his own findings.

Abt[94] described his experiences with potassium chloride in twenty-seven allergic patients, most of whom were children. Of this number Abt separated thirteen who had seasonal hay fever or hay fever with asthma. Eight of these thirteen were improved. Fortunately for the critical evaluation of the results, one reads in the author's tables that in these seasonal cases the earliest date at which the salt treatment was instituted was October 20. A therapeutic procedure which depends on its use after October 20 for its success in hay fever in the Chicago area is of highly dubious worth.

Harley[95] of England has also tried potassium chloride in allergic conditions. Not one of the ten hay fever patients was improved. Of the other thirty-three allergic patients, four were improved and six made worse, figures which are within the usual limits with any therapy in

these types of allergic complaints. We[96] have made a rather complete investigation of potassium salts in more than 150 cases of hay fever and have been forced to the conclusion that these salts are practically valueless in this condition.

The battle of oral pollen therapy has been fought on many fronts in the past year. Black[97] was again led to investigate this type of treatment, during the 1938 season. Treatment was coseasonal and was given to a group of forty patients with ragweed hay fever. The initial dose was 500 pollen units daily, which was increased by the same amount every day until 4,000 units were reached, or until symptoms subsided. Of this group, twelve patients (40 per cent) obtained improvement. The author does not regard the treatment as satisfactory. In three patients in whom it had not been possible to give hypodermic medication on account of severe reactions, the oral therapy enabled the hypodermic treatment to be resumed without difficulty.

In the 1938 season, London[98] treated forty-two ragweed patients with a combination of oral and hypodermic therapy. Of these, twenty-three had been treated hypodermically in 1937. Both the oral and injection therapies were given preseasonally. The maximum oral doses were around 100,000 pollen units. The results indicated that the ingestion treatment did not improve the anticipated results with the hypodermic therapy. Zeller[99] found that, after pollen ingestion, ragweed pollen absorption could not be demonstrated on passively sensitized skin sites. One gram of ragweed pollen ingested failed to give sufficient ragweed allergen in the serum to be demonstrated by test on (1) ragweed-sensitive persons and (2) sensitized sites of another person. It will be recalled that in a previous communication we had shown that even 5 Gm. of pollen after ingestion failed to produce enough allergen in the circulation to cause reaction on strongly sensitized sites. In twenty-two cases treated by Zeller with oral pollen alone five obtained satisfactory results. This author also describes many untoward reactions from this mode of therapy.

In an editorial summary Forman[100] emphatically states that oral pollen therapy is unsatisfactory, that there is no evidence that by its use expected relief will be obtained, and that gastrointestinal reactions are common. He concludes that oral pollen therapy as used today is not a substitute for the established method now in use. We may add that another attempt at experimentation with oral therapy in the summer of 1939 gave us no better results than those we obtained in the summer of 1937.

CAUSATIVE THERAPY

The results of pollen treatment in a group of 314 ragweed-sensitive patients over a five-year period were analyzed by Dundy and his associates.[101] They found that the sex, route of administration, and degree of skin sensitiveness had no influence on the outcome. Satisfactory effects were obtained in 84 per cent, of whom 5 per cent had perfect, and 79 per cent good, results. The percentage of satisfactory cases definitely increased with the increase in the maximum dose. The perennially treated cases showed a higher percentage of satisfactory results than those treated preseasonally. The authors attributed the superiority of the perennially treated group chiefly to the employment of higher doses in this group. Caution must be exercised, however, in any comparison of hay fever results with maximum doses. Cognizance must be taken not only of the fact that these are higher dosed patients receiving high doses, but that, apparently, they are the type *which is able to tolerate high doses.* The question arises then: Do these patients obtain better results because they have *received* high doses or because they belong to that class of persons who can be more easily desensitized (immunized?), perhaps even with smaller doses? It is evident that a different set of statistics will be required to answer this question.

Abramson[102] treated four ragweed patients during the hay fever season by electrophoresis of a ragweed solution on the skin. The treatments were given twice weekly, and good results were obtained. The author believes that this method may be advantageous in that the material deposited in this manner may persist in the skin for several days before it is finally absorbed. The increase in pollen doses by a more uniform rate is believed by Sternberg and Rosenthal[103] to constitute an important precaution for the purpose of limiting constitutional reactions. Their method as outlined contains nothing new and, no doubt, is the general scheme used by the vast majority who are conversant with pollen therapy.

During the course of treatment of forty hay fever patients by Greene,[104] 100 constitutional reactions resulted. These reactions are analyzed by this author as having occurred seven times after the first dose, twenty-six times after a change to the extract of increased strength, and sixty-seven times after increased doses without change in the strength of extract. The author believes that these results indicate that reactions cannot be blamed upon changes in the dilution of the extract. It appears to us, however, that the figures have been incorrectly analyzed. In treating hay fever patients, one gives a much smaller number of doses with changing dilutions than of those of the same strength. Assuming that each patient received thirty injections with three dilutions of the extract (two changes in strength), we obtain the following figures:

	NUMBER OF INJECTIONS	REACTIONS	PERCENTAGE OF REACTIONS
After first dose	40	7	17.5
After dose with change of dilution	80	26	32.5
After increased dose, without change in dilution	1,080	67	6.2
Total	1,200	100	8.3

From this analysis it is quite evident that the greatest percentage of reactions, on the basis of the actual number of injections in each group, occurred when the dilution of the extract was changed.

Infectious asthma in fifty-three children was treated by Stevens[105] with filtrates of the usual bacteria found in the respiratory tract. Beginning with a 1:100 dilution, the doses were increased, until finally the concentrated original material was injected. Of this group of children, fifty have obtained satisfactory results. Crump[106] has employed autogenous vaccines, obtained bronchoscopically, in the treatment of one hundred and twelve cases of asthma in children. Two-thirds of the patients had purulent tracheobronchitis. Vaccine alone was given in twenty-seven cases, while the remainder had various types of allergic management in addition. The impression gained by the author was that the vaccine was a valuable aid in the therapy.

Autogenous vaccines, mostly of the *Streptococcus* type and obtained from the respiratory tract, uterine cervix, rectum, and other possible foci of infection, were used by Ylvisaker[107] intravenously in the treatment of a small group of cases of asthma and other allergic conditions. The author believes that the bacterial type of asthma is similar to other forms of allergic asthma, and that the beneficial results obtained are due to specific desensitization.

In addition to the usual dust precautions, an air cooling, warming, and humidification system was installed in a hospital room by Osgood.[108] The outside air was filtered through a replaceable cotton and gauze filter. In such a room asthma due to inhalant factors has shown marked and prompt relief. This can be used also as a diagnostic method to differentiate inhalant asthma from other types.

SUNDRY FORMS OF TREATMENT

Iodized oil given intratracheally for asthma is becoming outmoded, it appears. However, a favorable report emanates now and then. Tewksbury and Fenton[109] have obtained satisfactory results in forty-three of fifty cases of bronchitis and bronchiectasis. They believe in the use of small doses of the oil, and they have not had any untoward effects. It should be remembered, of course, that their work was not concerned with asthma. Fuchs[110] reports spontaneous pneumothorax

in an asthmatic patient treated with iodized oil. In all fairness, it should be said that his paper does not contain definite evidence that the pneumothorax was due to the oil instillation.

Moore[111] treated thirty-five cases of asthma with iodized oil and concluded that his results were not encouraging. He found that those patients with bronchiectasis or productive cough were more likely to be benefited. He listed many contraindications to this form of treatment and warned that, despite all possible precautions, the procedure may be dangerous.

Criep[112] summarized the results obtained by him with iodized oil treatment in seventy patients with intractable asthma. Only ten benefited by this method, and the results were usually of a temporary nature. In some instances, good results were obtained by these patients with other procedures. Fifteen patients were treated with installations of unmedicated peanut oil, and temporary improvement was noted in three. The author cited many reactions, complications, and one case of fatal pneumonia from the use of iodized oil.

Barach and Swenson[113] studied the effect on the size of the bronchial lumen when air was breathed under a positive pressure of from 5 to 8 cm. of water. Their observations were made by means of roentgenograms after iodized oil instillation. It was found that, at the end of expiration, the bronchial lumina were from 1 to 2 mm. wider with breathing under positive pressure as compared to breathing with normal pressure. The inference is that, not only with helium, but also with ordinary air, increased pressure may aid asthma. Helium as a useful agent in status asthmaticus has been recommended also by Metz and his co-workers.[114]

It is claimed by Joseph[115] that he used insulin successfully for many years in the treatment of hay fever and asthma. The usual dose was 8 units every two to three days, for six doses, followed by a rest period of six days. In seven children with asthma not benefited by other treatment, Vollmer[116] gave injections of insulin every other day, beginning with 5 units and increasing to 40 units. Usually from fifteen to twenty-five injections were given, and shock symptoms were controlled by sugar administration. Although the author does not claim any cures, good results were obtained and often persisted following the series of treatments. He explains the effects on the ability of insulin to stimulate epinephrine secretion.

Suprarenal concentrate given orally was found of great benefit by Hipple[117] in ten cases of allergy.

Maytum and Leddy[118] present a further report on the roentgenologic treatment of asthma. They treated 161 patients with moderately severe or severe asthma and obtained the following results: marked relief in 24 per cent; moderate relief for periods of from one to many

months in 16 per cent; marked relief, but also with aid of other treatment, in 14 per cent; and less than 50 per cent relief in 46 per cent of the patients. Most of the patients were those in whom no specific cause was discovered or in whom no other management succeeded.

The late results of eleven cases of stellectomy for the relief of asthma were analyzed by Leriche and Fontaine.[119] In five of them improvement failed to occur; in six the results were good. One had complete absence of symptoms for thirteen years, and another, for over seven years. A third patient had complete absence of symptoms for seven years, followed by partial relapse. In the three other patients improvement still persisted after periods ranging from two and one-half to five and one-half years.

Considerable interest has been aroused recently in connection with the therapeutic possibilities of histamine and histaminase. Roth and Rynearson[120] found that histaminase prevented the allergic reactions in a case of insulin sensitivity. They subsequently applied their therapy in eleven other similar cases with varying results. In addition, they found that small doses of histamine in increasing amounts given twice daily were effective. Reference has already been made to Ertl's[9] report, in which he claims good results in hay fever by nasal treatment with a spray of histaminase solution. As a result of their experiments on guinea pigs, Karady and Browne[8] concluded that their work afforded evidence supporting the therapeutic use of histaminase.

This form of therapy for allergic conditions is being heralded to the profession and to the public by advertising and by newspapers. Favorable clinical data from known dependable sources are still in the minority. Until such time as well-planned and carefully controlled series of cases are reported, it would be well to maintain a healthy skepticism.

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Society Proceedings

SYMPOSIUM ON ALLERGIC DERMATOSES*

MARION B. SULZBERGER, M.D., PRESIDING

(Continued from issue of January, 1940, p. 210.)

Fungus Allergy. SAMUEL M. PECK, M.D., New York, N. Y.

I know of no greater advance in dermatology in recent years than the conception of allergy as playing a role in fungus eruptions. Dermatologists have come to recognize that the same organism, whether a bacterium or a fungus, can give rise to totally different syndromes, while unrelated pathogens can initiate practically identical clinical pictures. Skin eruptions due to microorganisms can be divided into two classic types: those typical forms which are due to the fungi themselves, and those atypical forms which only recently have been recognized as belonging to this group. This latter manifestation of fungus infection is referred to as cutaneous microbids. These depend for their development on the interaction between bacteria, fungi, or their products and the allergic skin. This allergy is due to an acquired hypersensitivity to microorganisms or their products which develops after the disease process has existed for some time. Classic examples of cutaneous microbids are the tuberculids, trichophytids, and levurids. By trichophytids, we mean the general term which has been applied to the microbid associated with fungus infections.

It must be borne in mind that both the epidermophyton and trichophyton fungi grow in the nonliving layers of the skin and its appendages. Marked inflammatory reactions do not develop until the living structures are invaded. The hypersensitivity with its resulting allergic manifestation is brought about by the invasion of the fungi into the living structure. It is for this reason that a sine qua non for the development of a trichophytid is a hypersensitivity to fungi or their products. This sensitivity is revealed by a positive trichophytin reaction. It is indeed fortunate that the trichophytin test represents a group reaction in the majority of instances. This means that the test does not usually have to be made with the identical fungus causing the lesions. The hypersensitivity to fungi develops after the primary infection has existed for some time. The period between onset of infection and development of hypersensitivity varies from a few months to several years, depending upon the type of fungus, the site of the primary infection, and the infected person.

Continuous maceration which is frequently seen between the toes, other traumatic moments such as treatment with strong ointments, or

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even x-rays force the fungi or perhaps their products into the blood stream. These in turn, coming in contact with the hypersensitive skin, give rise to trichophytids. It is now recognized by most dermatologists that, once the hypersensitivity develops, even the primary epidermophytosis contains in its clinical manifestations elements of fungus hypersensitivity, that is the tricophytid.

If we were to assume that the living organisms actually invade the blood stream, as seems to be borne out by some of my own positive blood cultures in cases of epidermophytosis, the circulating organisms are changed by contact with the blood serum and probably reach the skin in an attenuated state. To reach the keratin layer, that is, the dead tissue in which they can grow, they pass through the living structures which have become hypersensitive. The resulting interaction destroys the majority of them and gives rise to the trichophytids. If any organisms pass through these barriers and reach the dead tissues, they can be demonstrated in the trichophytids. This is rather a rarity.

If we were to assume, however, as is probably the case, that not only the fungi themselves, but also the toxins, can give rise to the allergic manifestations, we have a ready explanation for the fact that trichophytids are usually sterile. Up to the present, it has not been possible to demonstrate such circulating toxins. It is also within the realm of theoretical possibility that contact with primary lesions can cause transportation of the organisms to other parts of the body and give rise to trichophytids once the living tissues have been invaded. The eruptive character of most of the microbids speaks against such a conception, however. But such possibilities must be borne in mind when nonsymmetrical isolated lesions are found which are considered trichophytids, especially those in which the organisms are more readily demonstrated.

Since the attention of physicians has been focused on the microbids, the diagnosis is being made with great frequency and very often without proper supporting evidence. Experimental and clinical research has established certain definite criteria which must be present to support such a diagnosis. I would like to quote such criteria which I have presented in a previous communication:*

"1. The causative organism must be demonstrated in what is recognized by everyone as a classical manifestation of the disease.

"2. While it is not absolutely essential, the organism which is cultured from the primary lesion should be pathogenic.

"3. A positive reaction analogous to a tuberculin or a trichophytin reaction must be present.

*Allergic Manifestations of Fungus Diseases, New York State J. Med. 36: 1237, 1936.

"4. What is considered to be microbid should be seen as a frequent accompaniment of the primary lesion.

"5. Positive blood cultures for the same organism isolated from the primary lesion must be obtained, since it is admitted that most of the microbids are hematogenous eruptions. This is necessary because there is no reliable method of demonstrating the presence of circulating toxins.

"6. The microbids must develop subsequent to the primary infection.

"7. The microbids must be sterile usually.

"8. A support for the conception of a skin eruption as an "id" lies in certain clinical characteristics:

a. Appearance of the "ids" in showers;
b. Tendency to symmetry in distribution because of hematogenous origin;
c. Tendency to spontaneous involution after healing of the primary focus;
d. Focal reactions after injection of sufficient amounts of microbidin."

The type of trichophytid which develops, once the hypersensitivity to fungi or their products has become manifest, will depend a great deal on the localization of the embolized fungi and the site of greatest skin sensitivity. This localization plays a very important role in the morphology of the resulting trichophytid.

The trichophytids have been classified under four headings which can be grouped into the following outline:

I. Epidermal trichophytids (epidermis mainly involved)
  A. Eczematoid (dyshydrotic)
  B. Lichenoid
  C. Parakeratotic
  D. Psoriasiform
II. Cutaneous trichophytids (papillary body mostly involved)
  A. Diffuse forms
    1. Scarlatiniform exanthemas and enanthemas
    2. Erythroderma
  B. Circumscribed and disseminated forms
    1. Follicular localizations, usually lichenoid
    2. Not exclusively follicular
      a. Macular, papular, and even exudative eruptions
    3. Erysipeloid
III. Subcutaneous trichophytids (nodules found in the hypoderm of the type of erythema nodosum)
  A. Acute resolving form
  B. Destructive chronic form
IV. Vascular trichophytids
  A. Migrating phlebitis (venous)
  B. Urticaria (capillary)

Since the almost universal distribution of fungus infection has become so well recognized, the trichophytin test has become more and more important. Unfortunately, its interpretation has been disregarded to some extent; I mean its proper interpretation.

I do not believe that it will be denied by any workers in this field that the trichophytin test is specific. Proper evaluation of the trichophytin test takes into consideration, not only the reaction itself, but the reaction at a distance, namely, what happens as far as the focal reaction is concerned. In the classic examples of trichophytids, especially those in which we have a fungus infection of the feet with dyshydrotic or eczematoid eruptions on the hands, the proper evaluation of the trichophytin test is only important in degree. That is, it is a sine qua non for the diagnosis of a trichophytid that we must have a positive trichophytin reaction. If we consider the manifestations as representing very active trichophytids, then we must have a strongly positive trichophytin test.

It is little known, however, that very often in the more unusual types of trichophytid—namely those which resemble pityriasis rosea, those which are more eczematoid in type, and those which are somewhat erysipeloid—the trichophytin test simulates the actual trichophytid. This statement, however, is more nearly true of the more chronic type of trichophytid than it is of the acute exanthematic form.

One finds that the reaction to the tricophytin test is not always the same in degree throughout the year. If one were to test a patient with trichophytin at various times during the year, in many instances the test would become practically negative at the time when there is very little clinical activity. Perhaps this principle might be of importance in evaluating the tuberculin test also. In a number of instances, in testing persons with trichophytin at various times during the year, I have found that the test was more strongly positive during periods of exacerbation of the primary focus than at other times.

False positive reactions are not due to too great a concentration of trichophytin. Once we have a sensitivity to fungi or their products, the degree of intensity of reaction will depend, of course, on the degree of hypersensitivity, but also it will depend to some extent on the concentration of the trichophytin used. If a more concentrated trichophytin extract is used for the test, a greater skin reaction will develop, but it will not be nonspecific in the sense that the skin reaction is due to the concentration of the trichophytin alone. In the presence of a negative reaction to the same concentration of media as that represented by the more concentrated trichophytin extract, I have never seen a false positive reaction. False positive reactions with the trichophytin test are very often due to secondary bacterial contamination or, as has been mentioned previously, to the ingredients of the

media themselves, which are primarily toxic or irritant when given in too great a degree of concentration. Proper control will obviate such false positive readings.

It is best to read the trichophytin test within forty-eight hours, as in hyperreactive skins, which might tend to give false positive reactions or false positives due to irritants in the media, the reaction very often disappears at the end of that period. The immediate reaction which has been described recently in the literature is very rare in my experience. I have seen very few of them corresponding to ordinary whealing as is seen in hay fever type of sensitivity.

Patients manifesting primary urticarial reactions after injection of trichophytin usually do not have the ordinary delayed type of reaction. In one instance in which I did see such a reaction, it was associated with symptoms which were almost of an anaphylactic reaction. In about a half hour after the test dose of trichophytin, the patient developed angioneurotic edema with edema of the glottis and a mild form of shock, and adrenalin and other supportive measures had to be administered. This patient did not develop the ordinary type of trichophytin test and showed an absolutely negative test site in twenty-four hours.

It is also important to remember that when the trichophytin test is markedly positive, it of course denotes a high degree of sensitivity to the fungi or their products. This usually means that even the primary focus consists mainly of trichophytids. Because of this it is very difficult to find fungi from many of the lesions; one has to have a great deal of experience in attempting to demonstrate fungi to be sure that, when a scraping is taken, it is from epidermophytosis instead of an epidermophytid.

Recent literature, both foreign and American, has become increasingly filled with the discussion of levurids—those mycids which are due to *Monilia*. Ravaut, a pupil of Sabouraud, described the first cases. Very interesting examples of such eruptions have been demonstrated by Ramel, Hopkins, Sulzberger, myself, and others. One of the chief stumbling blocks seems to have been to prove a pathogenic role for *Monilia* cultured from what is called the primary lesions. It was difficult to be certain that the reaction following the intradermal injection of oïdiomycin was based on true hypersensitivity because of its practically 100 per cent incidence in the adult. However, in studying a group of infants and children I found that the supporting proof for such a conception could be found in such persons. Young infants and children rarely show a positive oïdiomycin reaction, but in the older age group the tests gradually reached an incidence of nearly 100 per cent. This shows that, because of the universal distribution of

this organism with accompanying universal infections and its high sensitizing potentialities, most of us probably finally develop a positive oïdiomycin test.

The only discussion of treatment I wish to take up, because of the shortness of time, is the question of the use of trichophytin as a therapeutic measure. It is admitted by nearly all workers in this field that the results have been somewhat disappointing; I, too, was discouraged until recently. However, I now realize that the inadequacy of our treatment was not due to the method or to the conception of the use of trichophytin, but rather to the trichophytin which has been available for this procedure. It has always seemed to me a paradox that, if we desensitize a patient to trichophytin, we are removing one of the barriers set up by the body against the dissemination of the fungi.

If, as has been mentioned previously, the trichophytids are due to a hematogenous dissemination of the fungi, then, if we remove the reaction of hypersensitivity, we are removing one of the mechanisms set up by the body apparently to kill the fungi as they reach the site where they develop. However, in many instances we do see improvement with injections of trichophytin. There must be some fundamental conception which has been inadequately explained to account for the improvement of patients with trichophytids by the injection of trichophytin. There also, in addition, must be some fundamental factor to explain the lack of good clinical results in the very patients in whom some desensitization is easily brought about.

It would be very important to know if a negative trichophytin test which develops by injection of trichophytin in a suitable person is brought about by a mechanism such as anticutin. This is important because in such a mechanism we are not actually removing a barrier which the body has set up to protect the organism against fungus infection; but we are rendering the patient anergic, which is just another expression of a greater degree of immunity, if you will, in producing substances which not only do away with protection against the organism itself, but which neutralize those toxins which specifically produce the reaction of allergy.

DISCUSSION

DR. SULZBERGER.—I should like to say a word before I open Dr. Peck's presentation for general discussion.

There is a chronologic variation in tuberculin sensitivity entirely similar to the one he described in trichophytin sensitivity. Moreover, there are many very interesting parallel immunologic findings in relation to both tuberculin and trichophytin sensitivity, whether or not one knows their exact significance. One fact which seems to me to be of great interest is that one can, by repeated intracutaneous injections of

either tuberculin or trichophytin, specifically reduce the degree of the skin sensitivity to the respective extract in a great many of the sensitive individuals, if not in all of them. Sometimes the accompanying disease produced by the specific microorganisms seems to be benefited by such desensitizing procedures.

DR. GEORGE H. CURTIS, Cleveland.—In regard to dermatitis on the hands, it is my impression that a majority of the cases require differentiation between epidermophytids, contact dermatitis, and the so-called nummular eczema of Pollitzer. I have found that epidermophytids on the hands usually disappear when an epidermophytosis elsewhere is eradicated. Very often, however, the three dermatitides so closely resemble one another, and search for the cause of the dermatitis by repeated contact and epidermophytic studies fails, that I am at a loss as to what further studies should be made. I should like to ask Dr. Peck whether he has found oïdiomycin or trichophytin to be of value in the differential diagnosis, including use of the extracts as a therapeutic test.

DR. PECK.—It is very important to evaluate the trichophytin test correctly. A negative trichophytin test is of importance because we can say with reasonable assurance that in such cases we are probably not dealing with trichophytids.

DR. CURTIS.—May I add more to that? Since positive skin tests with oïdiomycin are much more frequent than positive tests with trichophytin in nummular eczema, is the oïdiomycin of any value or of more value than trichophytin in the differential diagnosis?

Further, microscopic examination of the scales from nummular patches on the dorsa of hands, wrists, or forearms occasionally shows a yeastlike body or a yeastlike cell having a small hypha. I am undecided whether or not this is a true fungus or an artifact; however, when the scales are cultured, oftentimes a yeastlike growth is obtained. Also, in the case of nummular eczema, hyposensitization may be obtained with oïdiomycin as evidenced by a negative intracutaneous test, but the eczematous lesions persist. What is your opinion as to the relation between nummular eczema of Pollitzer and fungus infection?

DR. PECK.—I really am not sure how to evaluate this reaction. It is my belief along with many other dermatologists that there is such a condition as moniliasis with monilids. I also am reasonably sure that the oïdiomycin reaction is a specific one. In very young persons, that is, those below 10 years of age, a positive test with an extract such as oïdiomycin has clinical significance because there are many negative tests for that age group. But above 10 years of age there is an almost 100 per cent incidence of positive reactions, and, therefore, it is very difficult to evaluate such a reaction in connection with clinical manifestations. Also, while the oïdiomycin reaction does vary in cases, it does not give as much of a variation as a trichophytin test, nor does it tend to simulate a trichophytid after the local intradermal reaction as the trichophytin reaction does in many instances.

Many dermatologists believe that Pollitzer's nummular eczema has a parasitic etiology. I do not mean by that that it is necessarily due to either fungi or *Monilia;* even ordinary staphylococci or streptococci

might be the initiating organisms. It has never been proved that peculiar mycelia-like forms which are often isolated from scrapings from Pollitzer's nummular eczema are true fungi. In most instances they have been proved to be artifacts. There has to be a certain amount of laboratory experience in evaluating scrapings for fungi. Very often an inexperienced laboratory technician will report positive findings of fungi when we are dealing with artifacts due to potassium hydroxide. It is for this reason that in my laboratory we train the men to examine for fungi with xylol. If the findings are negative, especially in the examination of hair and nails, then potassium hydroxide is the usual technique resorted to.

If every instance of maceration between the toes were called athlete's foot, or epidermophytosis, then indeed we would be approaching a statistic which would give us almost 100 per cent incidence for this condition. The trouble with the diagnosis of epidermophytosis of the toes is that, on clinical grounds alone, a diagnosis is made when very often we really do not have this condition present. A thorough and rather prolonged attempt should be made to demonstrate the fungi either microscopically or culturally before a case of maceration between the toes, without a very typical picture, is called epidermophytosis. One would have to recall the ease with which even experienced dermatologists have been lead astray by so-called mosaic fungi to appreciate the difficulty of direct microscopic diagnosis of fungus infection.

I think everyone will agree that most investigators feel that the so-called mosaic fungi are artifacts.

DR. MERLE M. MILLER, Philadelphia.—I should like to ask Dr. Peck if the hyposensitization treatments influence the primary lesion in any way. Does a remission or exacerbation of the primary lesion alter your course of injections?

DR. PECK.—Of course I have seen exacerbation of the primary lesion. Very often even in the primary lesion we have the presence of trichophytids, and when we see a vesicle suddenly converted into a pustule, we know that we are dealing with an exacerbation of the primary lesion with the development of pustular trichophytids.

DR. HARRY S. BERNTON, Washington, D. C.—What preparation of hyposensitizing material do you use?

DR. PECK.—Fortunately at present we use our own trichophytin. I have always relied on the preparations prepared by the Lederle Laboratories. While it is true that it gives a rather low incidence of reaction, at least we did not get any false positive tests. One must bear in mind that we must have an adequate concentration of trichophytin to elicit a proper reaction. I find that the 1:30 trichophytin gives us too weak a reaction, especially in those borderline cases where we have very little activity in the primary lesion. I think, too, that once the patient is found not to be sensitive to the media, one does not have to worry about using too strong a concentration of trichophytin or the elicitation of a false positive reaction.

DR. SULZBERGER.—For some years we, at the Skin and Cancer Hospital, have been standardizing the trichophytin and oïdiomycin extracts

for the Lederle Laboratories. We have been deliberately keeping the trichophytin relatively weak because we know what it can do in causing flare-ups and generalizations of eruptions when employed in certain very hypersensitive cases.

Dr. I. S. Kahn, San Antonio.—Would you consider an immediate ++++ wheal reaction to a 1:3,000 dilution of trichophytin or oïdiomycin of definite clinical sensitivity?

Dr. Peck.—In my experience I certainly would pay attention to a real immediate positive wheal reaction following the intradermal injection of fungus extracts. In the number of cases that I have tested, I have seen a real positive immediate reaction only in a few instances. Nearly every case develops some whealing after intradermal injection of trichophytin and even of the media itself, a reading which I take to be nonspecific. However, recently I tested a postgraduate student who not only developed an immediate reaction after the intradermal injection of trichophytin, but developed a generalized urticaria and an angioneurotic edema with generalized symptoms of shock. We had a great deal of trouble in reviving him. This was accomplished by the injections of adrenalin. I must say the experience was quite new to me and somewhat frightening. It very much simulated a shock reaction like that seen in some asthmatics after injection of proteins. This patient did not develop the ordinary delayed reactions of trichophytin. In the few instances in which I have seen a whealing after injection of trichophytin, there were only very few that also gave a delayed positive reaction.

Dr. Kahn.—I have a patient on hand who gives a ++++ immediate positive to a 1:3,000 dilution of trichophytin (Lederle) and oïdiomycin (Merck) and does so repeatedly.

Dr. Howard Osgood, Buffalo.—One of my duties is physician to a boys' school. Dr. Hopkins says that 25 per cent of so-called athlete's foot is fungus infection, or, at least, that he can identify it as such. I should like to ask Dr. Hopkins what the other 75 per cent of athlete's foot is.

Dr. Hopkins.—The fact that a man has a peeling of his toes and gets better by painting them with iodine is no indication that he has a fungus infection.

Dr. Sulzberger.—I think that only about 25 per cent of the cases today presumed to be athlete's foot are actually due to fungi. I estimate that about one-half of the remaining 75 per cent—or between 30 and 40 per cent of the total of eczematous foot eruptions—are instances of contact-type dermatitis from shoe leather, slippers, socks, rubber bath mats, fungicides, and particularly from the great variety of medicaments which have been applied because the patients were thought to have athlete's foot, or because they wanted to prevent athlete's foot. Pustular psoriasis, nummular eczema, dermatitis herpetiformis, other nonfungous microbids, and many other dermatoses can simulate athlete's foot and may account for the remaining cases often erroneously diagnosed as fungus infections.

DR. WILLIAM W. DUKE, Kansas City, Mo.—I fully agree with the essayists in what they have said about fungus allergy but would like to add a brief note upon a relationship between this and physical allergy. An individual in a state of reaction to a physical agent, such as heat, cold, or light, is hypersusceptible to infection with both fungi and bacteria.

I could mention many illustrations of this. For example, patients with a light dermatitis of the face often have chronic acne or fungus infection of the face. These may disappear if the patient avoids light or gains tolerance for it. Likewise, heat and effort cases frequently have infections with fungi or bacteria which disappear when tolerance for heat is gained.

One patient with acne and fungus infection of the exposed parts was excessively sensitive to mercury and to mercury vapor light and sunlight. The application of a pencil of mercury light to the skin for thirty seconds brought out a local area of eczema within twenty-four hours which required a daily dressing for more than one week and remained visible for one month. Mercury salts and amalgam filling material gave a similar local reaction to patch testing. This patient's mouth was fairly full of mercury fillings. She was treated by gradually increasing general exposures to mercury vapor light with marked improvement in general health and reduction in staphylococcic and fungus infections. She did not completely recover, however, until sodium thiosulphate was administered hypodermically. I had a somewhat similar case of fungus dermatitis due, I thought, to sensitiveness to mercury and amalgam fillings. In this patient the removal of one of her many amalgam fillings was followed by a serious general reaction to mercury that caused the patient to refuse further treatment.

Allergic Occupational Dermatoses. LOUIS SCHWARTZ, M.D., New York, N. Y.

If we are to confine ourselves to the concept that the term allergy should be used only in cases where exposure to the substance produces demonstrable antibodies, then the role played by allergy in the causation of occupational dermatoses is a comparatively small one.

Many cases of occupational dermatoses, seemingly due to allergy, can be explained by changes in working conditions, or variations from the normal in the skin of the worker, or by breaks in the defense mechanism of his skin, or, as Oppenheim says, by the sum total of the mechanical, physical, and chemical action of the worker's particular occupation upon his skin.

In a compilation of about 10,000 cases of occupational dermatoses made from the reports of the various State Compensation Boards, it was found that the large majority of occupational dermatoses are caused by primary irritants and that it is in the groups listed under plants, dyes, dye intermediates, rubber and its compounds, and vegetable oils, fats, and waxes, that we must look for our cases of allergic occupational

dermatoses. These groups in which most of the cases of allergic dermatoses are likely to occur comprise about 18 per cent of all the cases of occupational dermatoses in our compilation of 10,000 cases. However, not all the cases coming under these headings are of allergic origin, because even some of these substances are primary skin irritants; for instance, not all the dermatitis due to plants is of allergic origin because some of the essential oils of plants may be classed as primary irritants and because the dermatitis occurring among vegetable canners, which is classified in our list under plants, may be caused by the maceration of the skin with irritant fruit juices and not by allergy. Therefore, it can be said that allergy is the cause of less than 18 per cent of occupational dermatoses.

In allergic occupational dermatitis there is always a period of incubation, usually eight to twenty-one days, although it may be longer. Therefore, dermatitis which develops in less than a week after the worker is exposed to the irritant is usually not due to allergy acquired from that particular job. The date of primary contact with the irritant is more easily determined in industry than it is outside of industry. For instance, an attack of dermatitis due to poison ivy may occur at the end of a week end in the country; at first it may appear that the period of incubation was only two or three days, but we do not know when the initial contact and sensitization took place. It may have been the previous year or the previous week, but in industry we know much more definitely from the nature of the worker's occupation just when he came in contact with the irritant or sensitizer.

The patch test sometimes gives a rapid, although perhaps not altogether reliable, clue as to whether or not an occupational dermatitis is due to allergy. If the dermatitis was or is generalized, and the reaction to patch tests with great dilutions of chemical spreads, and the dermatitis, if still present, becomes exacerbated as a result of the patch test, or if areas of healed dermatitis light up anew following the patch test, or new areas of dermatitis develop and constitutional symptoms follow the application of the patch test, then allergy is probably present. When such cases are encountered in industry, passive transfer should be tried. The Prausnitz-Küstner or passive transfer reaction gives us positive proof of the presence of antibodies. This test, I am sorry to say, is very rarely performed in industry.

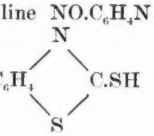
Occupational allergic dermatitis is usually seen among chemists and others who handle sensitizing chemicals. It is a well-known fact among chemists that many of the organic nitro compounds are sensitizers. Photographers handle developers, many of which are sensitizers; field workers come in contact with plants; florists, fruit and vegetable handlers, cannery workers, and insecticide makers, also come in contact with plant products and may develop allergic dermatitis. Rubber workers come in contact with sensitizing accelerators and antioxidants, and

munitions workers come in contact with sensitizing explosive compounds. Allergy to finished dyes, so often seen among the wearers of dyed clothing, is not common among the workers engaged in dye manufacture.

I have a list of chemicals here which, in my own experience, have produced what I considered might be allergic occupational dermatitis:

Rubber Accelerators:

Para nitroso dimethylaniline $NO.C_6H_4N(CH_3)_2$

Mercapto benzothiazole  (Captax)

Tetramethyl thiuram disulphide $(CH_3)_4(NCS_2)_2$ (Tuads)

Dyes:

Dinitrochlorobenzol $C_6H_3(NO_2)_2Cl$ (dye intermediate)
Paraphenylenediamine $C_6H_4(NH_2)_2$ (fur dye)
Amidoazotoluene hydrochloride (yellow dye)

Paint Preservative:

Phenyl glycide ether $(C_9H_{10}O_2)$

Explosives:

Tetryl $CH_3N(NO_2)_4$
T.N.T. $C_6H_5(NO_2)_3$

Insecticides:

Pyrethrum
Alpha naphthyl iso-thio cyanates

Synthetic Resin Manufacture:

Phenol C_6H_5OH
Formaldehyde H.CH.O

Laboratory Chemicals:

Acetonitrile CH_3CN
Michler's ketone $CO(C_6H_4N(CH_3)_2)_2$

Some of the men who worked with these chemicals were so sensitive to them that they could not go into the building where the material was stored without developing an itch. I consider such a sensitivity an allergic one.

Some chemicals are primary irritants in strong concentrations and sensitizers as well. Such chemicals are the chromates, many essential oils, and insecticides.

If we accept the fact that there is a definite period of incubation for the development of sensitivity, then it is possible for a worker exposed to these sensitizers to develop an allergic occupational dermatitis even three weeks after he has given up the job in which he was exposed to them. This is a very important medicolegal point because a worker may justly claim he developed an occupational dermatitis three weeks after leaving his last job.

Desensitization, as well as sensitization, occurs in industry. It is a well-known fact that in departments of chemical factories where skin irritants are handled, new workers at first usually develop a dermatitis on the exposed parts, but in most of them, if they keep on working, the condition clears up after a period of time. The workers become "hardened" as they call it; therefore, new workers who develop a dermatitis should not be taken off the job, but should be supplied with protective clothing and ointments and allowed to continue at their work, thus giving them time to develop an immunity. The immunity so developed lasts for a time after contact with the irritant has ceased. For instance, it lasts over the week end; it lasts after the factory shuts down for a few days or a week, but it usually fades out if the worker stays away from work for a month or more, so that when he resumes work after a long layoff, he must again go through the "hardening" process.

It seems that continuous occupational exposure first causes a sensitivity, and then, after the exposure continues, an immunity develops; or perhaps the worker becomes more careful in handling the chemicals after he discovers that they affect him. Workers who do not develop such an immunity should be transferred to other occupations.

Skilled workers, to whom a change of occupation means a large financial loss, should be given a chance to become immune by desensitizing injections. Attempts to desensitize by giving minute increasing doses of the sensitizing agent have met with success in only a few isolated cases. In view of the work of Landsteiner, Haxthausen, Sulzberger, and others, it is suggested that perhaps better results might be obtained by giving minute increasing injections of the sensitizer mixed with a protein such as egg albumen, fungus extracts, or the serum of the patient.

DISCUSSION

Dr. George H. Curtis, Cleveland.—Since Dr. Schwartz has an inside track on the manufacturing industry and the substances that are handled within the industry, I should like to ask him if we may call on him for assistance in obtaining the formulas and the ingredients of manufactured products from the industries that make them, thus aiding us in tracing contact dermatitis down to a single ingredient in a manufactured product.

Dr. Schwartz.—You can, and many dermatologists are doing so, and have done so, and we can in many instances tell the formula even without writing to the manufacturer, because we have many of these formulas in our office. However, some of the products on the market which cause dermatoses are made by secret formulas, and the manufacturers are not very willing to disclose what they contain; but if you will write me, I will write to the manufacturers and ask them to give that information and tell them that it will be used for scientific purposes; and, if they tell me, I will tell you.

DR. CURTIS.—In a case of dermatitis due to a dentifrice, the manufacturer gave me the ingredients to test but would not tell me what they were.

DR. SULZBERGER.—I have had a little experience of that kind and have developed a method which usually works. I had a patient who had a dermatitis from a nail-coloring material. (By the way, these dermatitides are usually on the face, very often on the eyelids or cheeks, where the backs of the nails touch the skin when the patient brings the hands to the face.) This case of nail polish dermatitis was proved conclusively by patch tests and by clinical trials. I wrote to the company and asked them to tell me the ingredients of the polish, and they categorically refused. They said that the whole affair was nonsense; that millions of women were using this nail polish; that there was no record of irritation, and that that was the end of the matter as far as they were concerned.

I then called up the company, repeated my request, and they banged down the receiver in my ear. I then called over again and said: "I have a case which I have proved to be due to an allergen in your nail polish. I am going to report that case in a medical journal. If you will not tell me the ingredients of your polish, I shall unfortunately be forced to include in my report the exact name of your polish and your company. I have no choice. If I cannot describe this polish by listing its ingredients and by discovering and naming the particular ingredient to blame, my only means of identifying the causal substance is by giving your trade name. But if you will be kind enough to furnish me with the names of the ingredients, I will be able simply to report a dermatitis caused by a nail polish containing such and such ingredients.

The next day the manager or the vice-president of the company was on the telephone; and they sent officials to see me and could not do enough to supply me with everything that I wanted.

The meeting was adjourned.

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., AND THEODORE B. BERNSTEIN, M.D., CHICAGO

Investigations Demonstrating the Hourly Variations of Air-Borne Fungi in Relation to Meteorologic Influences; Role in Crises. Alvarez, J. C., and Quintero Fossas, J. M.: Rev. de med. y cir. Habana **44**: 411, 1939.

The authors have made an atmospheric spore study of Havana in relation to hourly weather changes for a period of six days. While exposing culture plates for fifteen minutes every hour they kept record of the temperature, barometric pressure, relative humidity, wind velocity, and wind direction. They found that from 10 A.M. to 6 P.M. there were a larger number of molds. In order of frequency, the molds encountered were *Hormodendrum, Mucor, Penicillium,* and *Alternaria.* Greater barometric pressure, increased wind velocity, or increased temperature increased the mold count. The direction of the wind seemed to influence the variety, but not the quantity, of molds. In all their work the authors have attempted to correlate their findings with clinical observations.

Botanical Considerations of Some Pollens of Hawaii in Relation to Allergy. Roddis, L. H.: Tr. Hawaii Territor. M. A., pp. 75-81, 1939.

The pollens of Hawaii are discussed. The tropical plants, which are very numerous in the islands, are not common causes of hay fever since the pollens they produce are sticky, large in size, and have low toxic properties. One tree, the cycad palm, produces enormous amounts of pollen, but skin reactions have not been obtained with it. This palm is a gymnosperm, related to the forerunners of the conifers (pine).

Pollen counts were very low because of the insular position, high precipitation, and natural barriers; the count at Honolulu was 28. Consequently, less hay fever and asthma are encountered. The pollens most frequently causing trouble were: redtop, Bermuda grass, date palm, royal palm, algarroba, sugar cane, and mango. Those pollens which are produced in profusion but are not easily wind-borne still cause many cases of hay fever when the trees producing them are close to the house. The hibiscus flower, the emblem of Hawaii, which is used as a decorative flower and is worn in the hair by the women, has been responsible for hay fever in several cases.

On the Therapy of Hay Fever. Ertl, E.: Wien. klin. Wchnschr. **52**: 643, 1939.

Ertl believes in the efficacy of pollen treatment in hay fever, but speaks of the disadvantages. Previously he had tried histaminase injections in hay fever and admits that his results are not worth mentioning. Since it is thought by some that histamine release due to antigen-antibody reaction is responsible for allergic manifestations, the neutralization of the histamine formed at the site of the reaction might relieve the symptoms. In three hay fever patients in whom nasal application of pollen solutions had caused hay fever, he sprayed torantil (histaminase) solution one-half hour, one hour, and two hours prior to the pollen application. In all of these trials the hay fever symptoms were prevented.

Following this preliminary experiment he treated a series of twenty-three hay fever patients during the season with a spray of torantil. The contents of one ampoule were dissolved in from 0.5 to 1.0 c.c. of distilled water and sprayed into the nose. The frequency of administration was from semi-weekly to biweekly. In severe cases it was necessary to employ preliminary local medication. Of the twenty-three patients treated nine were freed from attacks and twelve were improved. In severe cases with generalized symptoms the additional use of torantil hypodermically was of help. In chronic vasomotor rhinitis the results were not good. The author explains this discrepant finding by the suggestion that, in the majority of cases of perennial rhinitis, the allergic reaction probably takes place elsewhere than in the nose.

On the Effect of Epinephrine on Blood Potassium. Brewer, G., Larson, P. S., and Schroeder, A. R.: Am. J. Physiol. **126**: 708, 1939.

Epinephrine causes an increase in serum potassium when injected into animals. In man, however, previous reports indicate that no such increase results. The authors point out that in animals potassium determinations are usually made on arterial blood, whereas in man venous blood is generally used. They were able to show that the transient increase in blood potassium evoked by epinephrine injection is considerably less in venous than in arterial blood. If only venous blood is examined, a slight increase may go unrecognized. They give findings of potassium determinations made in man from thirty to sixty seconds after epinephrine injection, which indicate an increase in serum potassium. They conclude that blood potassium concentration in man following epinephrine injection undergoes alterations identical with those observed in the experimental animal.

Dermatology

UNDER THE DIRECTION OF MARION SULZBERGER, M.D., NEW YORK, AND JOSEPH GOODMAN, M.D., BOSTON

Histology of the Frei Reaction. Franchi, F.: Gior. ital. di dermat. e sif. **80**: 369, 1939.

The author studied the histologic characteristics of the skin reactions to Frei antigen and other antigens (staphylococcus, streptococcus and gonococcus vaccines). In eight patients with lymphogranuloma inguinale, the reactions produced by the Frei antigen were tuberculoid in character. The nodular reactions which resulted from the nonspecific antigens showed an infiltration of lymphocytes, polymorphonuclear leucocytes, eosinophiles, histiocytes, and fibroblasts.

Dermatitides of Laundresses: Role of Chromium and Chlorine (in France). Rabeau, H., and Ukraineczyk: Ann. dermat. et syph. **10**: 656, 1939.

Javelle water, which is ordinarily considered a solution of sodium hypochlorite, also contains some potassium bichromate. Laundresses, cooks, housewives, and others who have developed dermatitis from the use of Javelle water were found in many instances to be sensitive to chromium salts. The authors, on the basis of their investigation of 200 cases, felt, however, that there was also sensitivity to chlorine. It is their belief that sensitization by the bichromate prepares the way for irritation by chlorine. It is not stated whether or not the sensitivity to chlorine was found to be allergic in these cases.

Occupational Dermatoses and Their Control. Strandberg, J., Bonnevie, P., Boström, G., and Hellerström, S.: Acta dermat.-venereol. **20:** 613, 1939.

This series of articles, too long and too detailed for summary here, presents an excellent review of the entire subject of industrial skin diseases. Especially to be recommended are Bonnevie's discussion of the etiology and pathogenesis of occupational skin diseases and Boström's discussion of patch testing.

Coccidioidin Skin Test. Kessel, J. F.: Am. J. Trop. Med. **19:** 199, 1939.

Coccidioidin is prepared by passing a killed culture of *Coccidioides immitis* through a Berkefeld filter. The filtrate in a dilution of 1:10 is used for the skin test. Twenty-six patients with proved infection gave twenty-two positive skin reactions. The four who reacted negatively were in advanced stages of the disease. Twenty-nine guinea pigs gave positive reactions after inoculation with the organism. Two hundred and twenty-eight patients with pulmonary tuberculosis showed positive reactions in only thirty-seven instances. Most of the thirty-seven patients who reacted positively were found to have lived in an area where they might have been exposed to coccidioides infection. Guinea pigs infected with tuberculosis were uniformly negative to the coccidioidin skin test. In general, the author found this skin test to be specific and to have the same significance as a positive tuberculin test.

Problems Concerning Pathogenesis of Allergic Eczemas, Elucidated by Experiments on Sensitization With Dinitrochlorobenzene. Hasthausen, H.: Acta dermat.-venereol. **20:** 257, 1939.

The application to the human skin of 30 per cent dinitrochlorobenzene in acetone produced a high degree of sensitivity, which made its appearance in most instances within two weeks after the first application of the chemical. Ultraviolet irradiation given one day before the sensitizing application of the 30 per cent solution did not prevent the development of hypersensitivity. However, freezing the area of sensitization with carbon dioxide snow immediately after the application of the 30 per cent solution prevented development of the sensitivity. In some instances, freezing the area of the first application as long as eight days after the use of the chemical still prevented the development of the sensitivity.

On human beings, the author isolated an area of skin by an incision through the cutis, but not down to the fascia. Sensitivity which was produced by application of the chemical in other areas of the skin spread to the isolated area. The author found that sensitivity appeared first in areas close to the site of the primary application and later in distant skin areas. These findings indicate that there is both local spread of the sensitivity in the skin and a hematogenous mechanism of transmission.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND MAX HARTEN, M.D., BROOKLYN

The Tuberculin Patch Test and the Mantoux Intradermal Test. Pearse, A. J., Fried, R. I., and Glover, V. A.: J. A. M. A. **114:** 227, 1940.

The Vollmer tuberculin patch test and the Mantoux intradermal test were compared in 624 children.

The tuberculin patch test was applied between the scapulae just to the right of the midline after the skin had been cleansed and defatted with acetone. The patch was removed in forty-eight hours, and the result was read ninety-six hours after application. Coincident with the application of the patch test, a Mantoux test with first strength purified protein derivative was performed on the forearm. This test was read forty-eight hours later, and, if this was negative, a second strength purified protein derivative Mantoux was done.

Eighty-seven per cent of the 624 children tested showed a complete correlation between the Mantoux and patch tests. Sixty-seven cases (9 per cent) were positive to the patch test alone, while only 21 (2 per cent) cases were positive to the Mantoux test alone.

The authors conclude that there is a high degree of correlation between the tuberculin patch test and the Mantoux test, and that the patch test is slightly more sensitive than the Mantoux.

Role of ''Auto-Antigens'' in the Pathogenesis of Physical Allergy. Karady, S.: J. Immunol. **37**: 457, 1939.

The present experiments were based upon the assumption that the exposure of the organism to a physical stimulus might lead to chemical structural changes in the protein of the plasm or cells which were sufficient to cause denaturation of the protein of the organism and, thus, to make it a foreign protein for that organism.

Guinea pig serum was exposed to cold (-5° C.) or to heat (56° C.) for one and one-half minutes and then allowed to return to room temperature. Guinea pigs, injected intra-abdominally with 3 ml. of this serum, were reinjected intra-abdominally three weeks later with 2 ml. of similarly treated serum. Marked anaphylactic symptoms developed in all animals except the group in which the serum reinjected had been exposed to the opposite physical condition. Exposure of guinea pigs' hind legs to cold (-5° C.) or to heat (56° C.), followed three weeks later by the intra-abdominal injection of 2 ml. of serum treated with cold or heat, resulted in anaphylactic shock in the correspondingly treated group, but not in the opposite group. Re-exposure to the same stimulus three weeks after exposure of the hind limbs to heat or cold also resulted in anaphylactic shock. The opposite stimulus produced negative results.

According to the author, these studies suggest a mechanism in the production of physical allergies by which the organism's own protein can be changed by various physical agents, so that it acquires antigenic properties and becomes an ''auto-antigen.''

Anaphylactic Shock in Animals With Different Degrees of Vitamin C Saturation. Diehl, F.: Klin. Wchnschr. **18**: 956, 1939.

The author reviews the literature on the effect of vitamin C administration upon anaphylactic shock and reports his own experiments.

Four series of female guinea pigs, sensitized during the summer months by intraperitoneal injections of horse serum on the first and fifth days, were shocked from twenty-one to twenty-five days later by the intracardial injection of 0.4 c.c. of horse serum. Animals in Series 1, 2, and 3 were fed a vitamin C-deficient diet. Animals in Series 1 received no additional vitamin C. Animals in Series 2 were injected intramuscularly with 20 mg. of vitamin C every two days. Animals in Series 3 received a similar amount of vitamin C daily. The animals in Series 4 were fed a diet rich in vitamin C, but received no additional vitamin C.

The vitamin C content of the adrenals, liver, and lungs was determined post mortem in all animals. In Series 1, a marked vitamin C deficiency was evident. The animals in Series 2 presented a slight deficiency. Series 3 and 4 showed a normal vitamin C content of the organs examined.

A relative vitamin C deficiency (Series 2) during sensitization resulted in a higher incidence of anaphylactic deaths than was noted with either a vitamin C-rich diet (Series 4) or a diet with additional large administrations of vitamin C (Series 3). Vitamin C deficiency (Series 1) and normal vitamin C content of tissues, obtained by a high vitamin C diet (Series 4), gave essentially similar results.

The author concludes that vitamin C has no definite effect on anaphylaxis in the guinea pig.

Species Specificity of Proteins of the Optic Lens. Markin, L., and Kyes, P.: J. Infect. Dis. **65:** 156, 1939.

Studies on the species specificity of proteins of the optic lens are reported.

Pigeons were used because they are easy to work with and because they survive anaphylactic shock. They were sensitized by intravenous injections of 1 c.c. of a 1:5 dilution of lens extract on the first, third, fifth, and nineteenth days. The animals were shocked fourteen days later by the intravenous injection of 1 c.c. of the specific antigen.

The authors note that beef and dog lens protein extracts were interchangeable in sensitizing and desensitizing pigeons. Pigeons highly sensitive to beef lens protein extract did not react to pigeon lens protein. Pigeons highly sensitive to beef lens protein showed no reaction to beef serum. Pigeons could not be sensitized with pigeon lens protein. Guinea pigs, however, could be sensitized with guinea pig lens protein extract.

Antibody Production in Response to Simultaneous Immunization With Two Antigens. Lui, S. C., and Wu, H.: Chinese J. Physiol. **14:** 87, 1939.

Quantitative studies of antibody production during simultaneous immunization with two antigens are reported.

Rabbits, sensitized by five courses of injections of crystalline egg albumen, were later sensitized by five courses of injections of crystalline egg albumen and horse serum albumin. Another series of animals, sensitized first with horse serum albumin, were later sensitized with both horse serum albumin and egg albumen. Control animals were sensitized by ten courses of injections of each of the antigens. A course of immunization consisted of three daily injections of 0.5 c.c. of a 1 per cent solution of the antigen, followed by a four-day rest period. Antibody production was quantitatively determined by washing the precipitin obtained and estimating the nitrogen content by micro-Kjeldahl tests.

The results indicated that, in rabbits, the antibody response to immunization with one antigen decreased when the animal was simultaneously immunized with another antigen. On the other hand, the total antibody production to simultaneous immunization with two antigens was greater than the response to immunization with either one of the antigens.

Histologic Lesions of the Nervous System in Rabbits in the Anaphylactic State. Baginski, S., Czarnechi, E., and Hurynowicz, J.: Compt. rend. Soc. de biol. **130:** 567, 1939.

Histologic studies of the nervous system were made following anaphylactic shock produced in rabbits sensitized by subcutaneous injections of horse serum.

Nystagmus and also cerebellar and vestibular symptoms were observed during anaphylactic shock.

Dilatation of the lymphatic vessels of the choroid plexus and enlargement of the Virchow-Robin spaces (the perineural spaces, the lymph vessels of the nervous system) in various regions of the nervous system were noted. Scattered necrotic areas in the tuber cinereum and hyperplasia of the adventitial cells of Marchand were also found. There were no pathognomonic lesions of the nervous system in the anaphylactic state.

Immunologic Investigation of Hypophyseal Mammotropic Preparations. Bischoff, H. W., and Lyons, W. F.: Endocrinology **25**: 17, 1939.

Mammotropic (lactogenic) preparations, made from beef or sheep pituitaries, were investigated to determine: (a) whether they were antigenic; (b) whether they were species-specific antigens; (c) whether the antibodies produced were capable of inhibiting their physiologic activity; and (d) whether their antihormone properties were species-specific.

The antigenicity of mammotropin was established by the production of typical anaphylactic shock in both actively and passively sensitized guinea pigs and by specific contractions of the uterine strip of sensitized animals in the Dale bath. The primary injection of up to 20 mg. of mammotropin produced no symptoms in twenty guinea pigs. Dale and anaphylactic studies indicated that neither beef nor sheep mammotropic preparations contained detectable amounts of the serum proteins of the animals from which they were obtained. The Arthus phenomenon could be demonstrated, especially after the third week, in rabbits sensitized by subcutaneous injections of either beef or sheep mammotropin.

Complement fixation and precipitin tests confirmed the results, obtained with the Dale technique, the Arthus phenomenon, and with both active and passive sensitization experiments, that mammotropic preparations, made from beef or sheep pituitaries, are antigenically indistinguishable and are not species-specific.

In pigeons, the crop-stimulating effect of beef and sheep mammotropin was neutralized by injecting the pigeons with sufficient dosage of antimammotropin serum, prepared in rabbits with either beef or sheep mammotropin. The mechanism of the antihormonal action of the antisera is not known to the authors.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Allergy of the Larynx (?). Chang, C. S.: Ann. Otol., Rhin. & Laryng. **48**: 783, 1939.

Two cases of what is considered to be allergic laryngeal obstruction, due to milk allergy, are reported. One is the case of a 3-week-old infant with a family history of allergy. The child had had diarrhea for six days and difficulty in breathing for two days. Laryngoscopy showed a moderately swollen and congested arytenoid mucous membrane, yielding pneumococci on culture. Leucocytosis without eosinophilia was present. A tracheotomy was done.

The second case was that of an infant 15 months old, with a history of asthma. His attacks lasted for from two weeks to two months. During one of these attacks he became cyanotic and was in extreme respiratory distress. The voice was hoarse and the breath sounds distant. Thymic enlargement was present. An

emergency tracheotomy was performed. Direct laryngoscopic examination revealed a moderate congestion of the epiglottis and a marked edema of the subglottic area. Eosinophiles were present in a smear of the exudate. Skin tests, including those for milk, were negative. In both cases decannulation was unsuccessful until a diet excluding milk was given. Following this, improvement occurred, and removal of the cannula was possible. A few days before dismissal, milk was again given and apparently tolerated.

Personality Differences in Allergic and Nonallergic Children. Riess, B. F., and de Cillis, O. E.: J. Abnorm. & Social Psychol. **35:** 104, 1940.

One hundred and thirty-nine allergic children from 8 to 16 years of age were submitted to the Pintner, Loftus, Forlano, and Olster personality test. This test measures ascendance, submission, extraversion-introversion, and emotional stability. A control group was afforded by 117 elementary school children, from 9 to 15 years old. The allergics, as a group, were more ascendant, more extraverted, and more emotionally unstable. The allergic group was subdivided into those with skin allergy, asthma, vasomotor rhinitis, and mixed allergy, and the scores of each group were statistically treated. Extraversion and instability do not tend to occur together in normal children, and in this respect, the allergic children appear to have an unusual personality constellation.

The Blood Picture During the Alarm Reaction. Dalton, A. J., and Selye, H.: Folia haemat. **62:** 397, 1939.

Acute damaging stimuli, such as exposure to cold, muscular exercise, toxic doses of drugs, hemorrhage, and surgical intervention, elicit the alarm reaction. This is a hitherto unrecognized general reaction of the body, which is nonspecific and includes enlargement of the adrenal cortex with a decrease in its lipid content, loss of chromaffinity of the adrenal medulla, acute involution of the thymus, lymph nodes, and spleen, formation of ulcers in the gastrointestinal tract, hemoconcentration, and characteristic blood chemical changes.

Using 4 per cent formaldehyde injected intraperitoneally or subcutaneously as the alarming mechanism in a small number of rats and rabbits, the authors feel they have shown that a leucocytosis preceded by a decrease, and followed by an increase, in eosinophiles is a constant feature of the alarm reaction.

Gastrointestinal Allergy in Children. Fries, J. H., and Zizmer, J.: J. Pediat. **16:** 69, 1940.

The authors describe the clinical reactions resulting from the oral or rectal administration of foods in thirty sensitive persons. The foods were mixed with barium sulfate, the group being one previously reported upon in regard to the roentgenographic findings. Nausea, vomiting, abdominal pain, and oral or pharyngeal symptoms occurred in this order of frequency after oral administration of the offending antigen. Abdominal pain, tenesmus, nausea, and sensation of fullness were the symptoms complained of after rectal administration. Three constitutional reactions occurred. Intracutaneous tests with an extract of the offending antigen were positive in 73 per cent of the cases, and usually markedly so.

Because of the severity of reaction following the rectal administration of the antigen, only one-half the group was studied by that method.

Rhinology in Children. Résumé of and Comments on the Literature for 1938. Wishart, D. E. S.: Laryngoscope **45**: 603, 1939.

In an interesting summary the author has chosen what he considers the most significant contributions in 1938 to the subject of rhinology in children. His own comments are not the least interesting portion of the text. The presence of unrecognized sinusitis, the dangers of benzedrine, the inability of anyone save a rhinologist to examine the nose, the advantages of conservatism in sinus surgery of the asthmatic patient, and the dangers in infants and very young children of pulmonary damage from nasal instillations are some of the subjects upon which he makes his position clear.

Skin Tests in the Study of Asthma and Other Allergic Diseases in Childhood. Becker, G.: Monatschr. f. Kinderh. **81**: 65, 1939.

This article is an account of five years' experience with allergic cases in a German children's hospital. At first, both intracutaneous and scratch tests were used, but soon the latter were dropped and only intradermal tests done. No serious reactions were encountered. Mixtures of related antigens were used for initial tests, which included bacteria, foods, fungi, pollen, environmental antigens, and human dander.

Seventy-eight per cent of the eighty-seven cases gave positive skin tests. Forty-three patients reacted to house and environmental antigens, thirty-three to bacteria, nineteen to animal danders, five to foods, and only one to pollen. The fall in blood eosinophiles during an attack and their rise following an attack were frequently noted.

It is concluded that the approach to the study of allergic diseases by way of history and skin tests is the method of choice.

Investigation of the Calcium and Phosphorus Content of Raw and Heated Human and Cow's Milk and Their Ultrafiltrates. Weingartner, L.: Monatschr. f. Kinderh. **80**: 157, 1939.

The phosphorus content of raw and sterilized milk is about the same, whereas heated human milk has 28 per cent less phosphorus than raw human milk. If the two forms of human milk are passed through the ultrafilter, the difference becomes 40.5 per cent. On the other hand there is almost no difference in the ultrafiltrate of the two forms of cow's milk. An organic acid phosphorus combination, as well as an inorganic acid phosphorus colloid combination, are assumed to account for this effect.

There is also a reduction in calcium which amounts to 19.3 per cent in heated human milk as compared with unheated human milk. If both forms are passed through an ultrafilter, this difference in calcium contents no longer exists. Heated cow's milk does not show any significant reduction in calcium content over the raw form. Mineral metabolism disturbances in premature infants fed sterilized human milk may rest on this basis.

Contribution to the Pathogenesis of Exudative Eczematoid. Hüllstrung, H.: Monatschr. f. Kinderh. **80**: 1, 1939.

In accord with the teaching of Czerny in regard to exudative diathesis, the cause of exudative eczematoid lesions is thought to be a disturbance in metabolism. That there is an alteration in the carbohydrate metabolism is indicated by the frequently found hypoglycemia. In contrast with eczema, exudative

eczematoid diathesis has a characteristic blood sugar tolerance curve consisting in a relative initial hypoglycemia, an absence of the hypoglycemic dip, a minimal sugar increase following adrenalin, and a negative summative effect with superimposed tests.

Assuming a neurohormonal regulation of carbohydrate metabolism, there would seem to be a partial hypofunction of the hypophysis, adrenal, and pancreas, as well as poor glycogen formation in the liver. This disturbance of internal glandular secretion is established early in life and may even be congenital. The signs of allergy which often accompany exudative eczema usually make their appearance in later years and probably are not closely related to the disease.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Cheilitis, Fixed Drug Eruption, and Gastrointestinal Allergy From Eosin Dye of Lipstick. Hecht, R., and Rappaport, B. Z.: J. A. M. A. **113**: 2410, 1939.

Hecht and Rappaport report a very interesting case of cheilitis with fixed drug eruption and gastrointestinal allergy from the eosin dye of lipstick. After a clinical investigation and patch testing, it was found that the symptoms were caused by the dye in a lipstick, tetrabromofluorescein. Upon avoidance of this preparation, the cheilitis and dermatitis of the face subsided. It is especially noteworthy that the gastrointestinal symptoms also subsided. It was finally concluded that the general use of lipsticks containing tetrabromofluorescein or similar dyes by American women may explain many obscure cutaneous eruptions, especially of the fixed type, and may explain some cases of gastrointestinal disturbances of the nature of spastic or mucous colitis.

Is the X-ray Examination of the Maxillary Sinus Superior to the Simple Transillumination? Waldapfel, R.: Laryngoscope **50**: 63, 1940.

Some difference of opinion has existed for some time as to the comparative value of transillumination and x-ray of the sinuses. It is generally agreed, however, that the x-ray is more exact and a more definite method of diagnosis. Waldapfel states that, in the simple transillumination, a difference in darkness of the maxillary sinus can be caused, not only by a disease of the sinus, but also by asymmetry of the two sinuses and varied thickness of the bone. These physiologic anomalies do not play a part in the x-ray examination and do not influence the results. He further points out that, apart from disease of the maxillary sinus itself, darkness in transillumination can be caused, not only by thickness of the bony walls and asymmetry of the maxillary sinus, but also by infiltration of the soft parts, even of the slightest degree. In such instances the transillumination may show more than the x-ray. Complete or massive cloudiness in transillumination with negative x-ray findings is to be regarded as significant of infiltration of the soft parts or subcutaneous edema or hematoma, even if no swelling or discoloration of the skin is evident.

Argyria Resulting From Intranasal Medication. Bryant, B. L.: Arch. Otolaryng. **31**: 127, 1940.

In the local treatment of nasal allergy, preparations containing silver salts are often employed. Prolonged use of silver salts may result in the production of

general argyria. Bryant reports the case of a patient who was treated daily for three months with a 10 per cent solution of mild protein silver in the form of Dowling packs for the relief of symptoms indicative of chronic ethmoiditis. Upon examination, the entire nasopharynx looked as though it had been sprayed with soot, and the nose showed that every millimeter of the mucosa was almost black. The only other areas of pigmentation were the finger nails and the conjunctiva of the lower lids. Several months after the discontinuation of the treatment with the silver protein, the nasal membranes had lightened considerably, indicating that absorption does take place directly from the site of application, despite the rather widespread opinion that the silver is absorbed only from the intestinal tract. Bryant suggests that reduction and absorption must occur at the site of application.

Relation of Allergy and Tonsillectomy in Children. Incidence of Respiratory Allergy in Cases of Routine Tonsillectomy. Hansel, F. K., and Chang, C. S.: Arch. Otolaryng. **31**: 45, 1940.

In the management of frequent colds, sinusitis, bronchitis, and recurrent pneumonia, Hansel and Chang emphasize consideration of allergy as a possible etiological factor. In an investigation of 200 children who were seen routinely for the consideration of removal of tonsils and adenoids, a definite diagnosis of allergy was established in twenty-six, or 13 per cent. Six of the patients had hay fever. It was further stressed that these cases of respiratory allergy may be overlooked unless an adequate history, physical examination, and cytologic studies are carried out in each instance. Removal of the tonsils and adenoids in allergic children should not be performed during a hay fever season, and the indications for operation should be the same as in nonallergic children. The tonsils and adenoids should not be removed with the idea of alleviating allergic symptoms.

Nasal Sinusitis and Asthma: A Thesis. Rackemann, F. M., and Weille, F. L.: Arch. Otolaryng. **30**: 1051, 1939.

Rackemann and Weille discuss the relationship of disease of the paranasal sinuses and asthma. In a large series of cases in which operative procedures were performed upon the sinuses, they found that, in general, the end results are often disappointing. Among the cases in which tissue from the antra was studied microscopically, pus pockets were found in the mucosa in about 10 per cent of the cases. No definite relationship was noted between the results of operative treatment and the degree of improvement of the asthma. They noted, for example, that in some instances asthma was relieved for months or years, but they state that the chances were almost nine out of ten that sooner or later the asthma would recur. Rackemann and Tobey emphasize the point that sinusitis is a part of the asthmatic syndrome, and not the cause of it. In about one-third of the new patients with asthma which they observed, operations had already been done on the nose or on the nose and sinuses. About one-half of the patients had lesions at the time of the examination. It was finally concluded that, if the nature of the sinal lesion indicates operation for itself without regard to the asthma, operative treatment will do good, but the good will be only partial and only temporary in most cases because the sinal lesion is a part of the picture and not a cause of it.